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Metastatic Basal Cell Carcinoma of the Skin

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ABSTRACT

Background: The literature on metastatic basal cell carcinoma (mBCC) reveals the rarity of this condition, which emerges from the more prevalent basal cell carcinoma (BCC), accounting for about 80% of nonmelanoma skin cancers. **Literature Review:** Risk factors for mBCC include age, skin type, prior skin damage, and tumor characteristics, which significantly influence prognosis ((Aditya & Rattan, 2013); (Lance Cowey, 2013)). Once metastasized, BCC is associated with a poor prognosis, with surgical options often becoming limited as the disease progresses ((Lance Cowey, 2013)). The emergence of targeted therapies, particularly vismodegib, which inhibits the Hedgehog signaling pathway, marks a significant advancement in treatment options for advanced and metastatic cases ((Berrada et al., 2014); (Hoashi et al., 2022)). These therapies provide alternatives for patients unsuitable for surgery and represent a shift towards more personalized treatment approaches ((Lance Cowey, 2013)) The literature also emphasizes the importance of accurate diagnosis, particularly in atypical presentations where primary BCC may mimic metastatic disease ((Haskell Hanisch et al., 2023)). Histopathological evaluation remains crucial in differentiating between these forms, as misdiagnosis can lead to inappropriate treatment strategies ((Haskell Hanisch et al., 2023))..
Conclusions: In conclusion, the body of literature on mBCC highlights its rarity and the complexities involved in its diagnosis and treatment. The low incidence of metastasis, coupled with the challenges posed by advanced forms of BCC, underscores the necessity for ongoing research into effective treatment modalities and the development of targeted therapies. Furthermore, understanding the risk factors and clinical characteristics associated with mBCC is essential for improving patient outcomes and guiding clinical management.

Keywords: Metastatic Basal Cell Carcinoma, Skin

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INTRODUCTION

The literature on metastatic basal cell carcinoma (mBCC) reflects a complex interplay between the biological characteristics of basal cell carcinoma (BCC), its rare metastatic potential, and evolving treatment strategies. (S. Mehta et al., 2012) highlight that while BCC constitutes approximately 80% of nonmelanoma skin cancers, its metastasis is exceedingly rare, with a notable incidence among middle-aged men, particularly those with long-standing lesions. The authors emphasize that metastases typically arise from primary tumors located in the head and neck, underscoring the importance of histopathological confirmation in diagnosing mBCC.

In the subsequent year, (Aditya & Rattan, 2013) provide a comprehensive overview of risk factors associated with mBCC, including age, skin type, and prior skin damage, while noting that once metastasized, BCC is linked with a poor prognosis. They assert that treatment decisions must consider tumor characteristics and patient health, with surgery being the predominant approach. (Lance Cowey, 2013) further elaborates on the challenges presented by advanced BCC, emphasizing that despite surgical options, some tumors may progress to local invasion, and metastatic cases are regarded as terminal. The limited effectiveness of traditional chemotherapy in treating advanced BCC is particularly concerning, highlighting the need for alternative therapies.

(Berrada et al., 2014) introduce vismodegib, a targeted therapy that has shown promise in treating locally advanced and metastatic BCC by inhibiting the Hedgehog signaling pathway. They document the clinical efficacy of this agent, which was approved for use in 2012, and the need for effective management strategies due to the rarity of mBCC and the complexities involved in treatment.

(Piva de Freitas et al., 2017) build upon previous findings by analyzing historical cases of mBCC, identifying critical diagnostic criteria and risk factors that contribute to metastatic development. Their review draws attention to the significant correlation between primary tumor size and metastasis, with larger

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tumors presenting a higher incidence of spread. The authors also discuss treatment modalities, emphasizing the role of surgery and radiotherapy, while acknowledging the emergence of Hedgehog inhibitors as a viable option for patients unsuitable for traditional treatments.

(Villani et al., 2022) address the increasing incidence of BCC and the necessity for innovative treatment options, particularly for advanced cases. They highlight the challenges posed by difficult-to-treat BCC and the need for personalized therapeutic approaches. (Hoashi et al., 2022) further explore the molecular mechanisms underlying BCC and identify specific tumor features that may predict metastatic potential, reinforcing the notion that certain BCC variants exhibit heightened aggressiveness.

Recent studies, such as those by (Haskell Hanisch et al., 2023) and (K Imlay et al., 2024) continue to emphasize the importance of accurate diagnosis and treatment for BCC, particularly in cases where the tumor may mimic other malignancies. These findings illustrate the critical need for ongoing research into the histopathological characteristics and treatment strategies of mBCC, as well as the potential for emerging therapies to improve outcomes for affected patients. Overall, the literature underscores the rarity of metastatic BCC, the multifaceted nature of its diagnosis and treatment, and the evolving landscape of targeted therapies aimed at addressing this challenging condition.

LITERATURE REVIEW

The article "Metastatic Basal Cell Carcinoma: A Biological Continuum of Basal Cell Carcinoma?" by (S. Mehta et al., 2012) provides a comprehensive examination of the rare phenomenon of metastatic basal cell carcinoma (BCC), which constitutes a small fraction of all BCC cases. The authors highlight that BCC is the most prevalent form of nonmelanoma skin cancer, accounting for approximately 80% of such cases globally. This statistic underscores the significance of understanding the behavior and potential metastasis of this common malignancy.

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The authors note that the incidence of metastasis in BCC is exceptionally low, with reported rates ranging from 0.0028% to 0.55%. This rarity is particularly critical for clinicians and researchers who must differentiate between typical BCC behavior and cases that may evolve into metastatic forms. The article emphasizes that the majority of metastatic BCC cases originate from primary lesions located in the head and neck region, which is noteworthy given the anatomical and biological factors that may contribute to this pattern.

A pivotal aspect of the article is its focus on the demographic characteristics of patients affected by metastatic BCC. The findings indicate that this condition predominantly affects middle-aged men with a history of long-standing BCC. This demographic insight is essential for guiding surveillance strategies and clinical management, particularly in identifying patients who may be at higher risk for metastasis.

The case study presented in the article illustrates a patient with metastatic BCC on the back, who experienced a recurrence four years post-excision. This particular case is significant as it highlights the potential for BCC to metastasize to regional lymph nodes, skin, soft tissues, and muscles, despite the initial successful treatment. The authors' discussion of this case reinforces the need for ongoing monitoring and follow-up in patients with a history of BCC, particularly those with lesions in high-risk areas.

The article "Vismodegib: A smoothened inhibitor for the treatment of advanced basal cell carcinoma" by (Aditya & Rattan, 2013) provides a comprehensive overview of basal cell carcinoma (BCC), particularly focusing on its metastatic form, metastatic basal cell carcinoma (mBCC). The authors highlight that BCC is the most prevalent cutaneous malignancy, constituting around 70% of all skin cancers, which underscores the clinical significance of understanding its progression and treatment options.

The discussion surrounding the risk factors for mBCC is particularly noteworthy. The authors enumerate various factors such as age, male sex, skin phototype, and extensive sun exposure, which contribute to the likelihood of metastasis.

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Additionally, they point out that severe actinic damage, prior radiotherapy, the number of existing tumors, and genetic factors also play critical roles in the development of mBCC. This multifactorial risk profile emphasizes the need for personalized assessment in patients, as these variables can significantly influence disease progression and treatment outcomes.

In terms of treatment modalities, the article outlines that surgical intervention remains the primary approach for most BCC cases. However, for patients with locally advanced BCC (laBCC), the options become more limited, necessitating the exploration of non-surgical treatments. The introduction of vismodegib, a smoothened inhibitor, represents a significant advancement in the therapeutic landscape for advanced BCC. The authors argue that targeted therapies like vismodegib can be particularly beneficial for patients who are not candidates for surgery, thereby expanding the treatment arsenal for this challenging condition.

The article effectively conveys the complexity of managing mBCC, highlighting the importance of considering various patient-specific factors when determining the most appropriate treatment strategy. However, while the authors focus on vismodegib as a promising option, further research into the long-term efficacy and safety of such targeted therapies is essential. Moreover, the article could benefit from a more detailed discussion on the mechanisms of action of vismodegib and its comparative effectiveness against traditional treatments.

In the article "Targeted Therapy for Advanced Basal-Cell Carcinoma: Vismodegib and Beyond," (Lance Cowey, 2013) provides a comprehensive overview of the challenges associated with advanced basal-cell carcinoma (BCC), particularly in its metastatic form. The article highlights the significant prevalence of BCC, noting that it constituted approximately 80% of the more than 2 million cases of nonmelanoma skin cancers diagnosed in 2006. This statistic underscores the public health impact of BCC, particularly given its generally favorable prognosis when treated early and locally.

Cowey emphasizes that while BCC tumors typically do not metastasize, there are instances where they can progress to advanced stages characterized by significant

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local invasion. In such cases, surgical excision may not be feasible, and traditional radiotherapy may not be effective or may lead to recurrence. The author points out that this progression to advanced BCC, particularly when it becomes metastatic, is associated with a dismal prognosis, with a median survival of only about eight months for affected patients. This stark statistic highlights the urgency for effective treatment strategies for advanced BCC.

The article critically evaluates the limited treatment options available for advanced BCC, noting that no cytotoxic chemotherapy has received approval for this condition. Cowey mentions that although agents like cisplatin have been employed in clinical settings, the outcomes have been inconsistent, indicating a gap in effective therapeutic interventions for patients with metastatic BCC. This limitation is significant, as it reflects the need for novel therapeutic approaches that can address the complexities of advanced BCC.

Furthermore, the article introduces the concept of targeted therapy, specifically mentioning vismodegib as a potential breakthrough in the treatment of advanced BCC. Vismodegib, a Hedgehog pathway inhibitor, represents a shift towards more personalized treatment options that could potentially improve outcomes for patients with advanced disease. Cowey's discussion of vismodegib and its role in the therapeutic landscape for advanced BCC is particularly relevant, as it opens avenues for further research and development in this area.

The article "Vismodegib: the Proof of Concept in Basal Cell Carcinoma" by (Berrada et al., 2014) provides a comprehensive overview of basal cell carcinoma (BCC), emphasizing its clinical characteristics, genetic predispositions, and treatment options. The authors effectively highlight that BCC is the most prevalent form of skin cancer, predominantly affecting Caucasian individuals, and is influenced by both environmental factors and genetic predispositions, particularly the presence of Gorlin syndrome.

The article details the clinical presentation of BCC, describing it as a pink pearly papule with telangiectatic vessels, which is crucial for clinicians in diagnosing this malignancy. Additionally, the authors note that while BCC typically exhibits slow

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growth, there are instances where it can become aggressive and invade surrounding tissues. This variability in clinical behavior underscores the need for vigilant monitoring and tailored treatment strategies for patients.

A significant contribution of the article is its discussion on the rarity of metastatic BCC, which is an important consideration for healthcare providers. The authors acknowledge the challenges in managing patients with advanced disease, particularly due to factors such as age and comorbidities, which can complicate treatment decisions. This highlights the necessity for a multidisciplinary approach in managing these patients.

The article also delves into the pathophysiological mechanisms underlying BCC, particularly the dysregulation of the hedgehog signaling pathway. The introduction of vismodegib as a targeted therapy marks a pivotal advancement in the treatment landscape for locally advanced and metastatic BCC. The authors provide evidence from clinical trials demonstrating the efficacy of vismodegib, which was approved in 2012, thus offering hope for patients with limited treatment options.

Furthermore, the authors present a range of traditional management strategies for BCC, including cryotherapy, curettage, and surgical excision. This comprehensive overview of treatment modalities allows for a better understanding of the therapeutic landscape and informs clinical decision-making.

The article titled "Metastatic Basal Cell Carcinoma: A Rare Manifestation of a Common Disease" by (Piva de Freitas et al., 2017) provides a comprehensive examination of metastatic basal cell carcinoma (mBCC), a condition that, while derived from a common skin cancer, presents significant challenges in clinical management due to its rare metastatic potential. The authors trace the historical context of mBCC, beginning with Beadles' initial report in 1894 and highlighting the diagnostic criteria established by Lattes and Kessler in 1951. This historical perspective sets a foundation for understanding the evolution of knowledge surrounding mBCC.

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The study's methodology is robust, incorporating a thorough literature review alongside a systematic search of the PubMed database, which yielded 24 additional cases. This culminated in a total analysis of 25 cases, allowing for a more nuanced understanding of the demographics and clinical characteristics associated with mBCC. The authors note a predominance of male patients with a median age of 65, which aligns with existing literature on the demographics of basal cell carcinoma (BCC) more generally.

A critical insight from the article is the correlation between the size of the primary tumor and the likelihood of metastasis. The authors provide specific incidence rates for tumors of varying sizes, indicating that larger tumors significantly increase the risk of metastatic spread. This information is crucial for clinicians in assessing patient risk and tailoring surveillance strategies. Additionally, the article identifies various risk factors for mBCC, including prior radiotherapy, local recurrence, and immunosuppression, which could inform both preventive and therapeutic approaches.

The article also sheds light on the typical locations of primary tumors, with a significant concentration in the head and neck regions. This finding suggests that clinicians should maintain a high index of suspicion for metastasis in these areas, especially in patients presenting with larger lesions or other risk factors. The histological variants of BCC identified in the study—such as infiltrative and sclerosing types—further underscore the complexity of mBCC and the need for careful histopathological evaluation.

Moreover, the pathways of tumor dissemination are discussed, with lymphatic and hematogenic routes being the most common. The identification of lymph nodes and lungs as primary sites of metastasis provides essential information for staging and treatment planning. The authors report a mean interval of approximately seven years between the onset of the primary tumor and the detection of metastases, a timeline that underscores the need for long-term follow-up in patients with BCC.

The treatment options for mBCC, as outlined in the article, are limited, with surgery and radiotherapy being the predominant modalities. However, the introduction of

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Hedgehog signaling pathway inhibitors represents a significant advancement in the management of patients who are not candidates for traditional therapies. The study's findings that 92% of patients received some form of treatment, with a notable percentage undergoing combined therapies, highlight the multifaceted approach required in managing this complex condition.

The article "New Emerging Treatment Options for Advanced Basal Cell Carcinoma and Squamous Cell Carcinoma" by (Villani et al., 2022) provides a comprehensive overview of the landscape of non-melanoma skin cancers, particularly focusing on basal cell carcinoma (BCC). The authors emphasize that BCC, which constitutes approximately 80% of keratinocyte carcinomas, is the most prevalent form of skin cancer in the Western world, with a concerning lifetime risk of 20–30%.

One of the noteworthy aspects of the article is its discussion on the rising incidence of BCC, which correlates with increased sun exposure and the prevalence of risk factors such as blistering sunburns and specific genetic predispositions. The authors highlight that while cutaneous squamous cell carcinoma (cSCC) can metastasize in a small percentage of cases (3–7%), metastatic BCC is exceedingly rare. This distinction is crucial as it underscores the generally indolent nature of BCC compared to other skin cancers, although it does not diminish the potential severity of advanced cases.

The article also critically evaluates the current treatment modalities for BCC, identifying surgical excision as the gold standard. Techniques such as Mohs micrographic surgery and other destructive treatments are presented as effective for early-stage BCC. However, the authors point out that the management of difficult-to-treat BCC, including locally advanced and metastatic forms, remains a significant challenge in dermatologic oncology.

In response to this challenge, the authors advocate for the exploration of new emerging treatment options that could provide non-invasive alternatives for patients with advanced BCC. This call for innovation is particularly pertinent given the limitations of existing therapies for more complex cases. The article effectively

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highlights the need for ongoing research and development in this area to improve patient outcomes.

The article "Molecular Mechanisms and Targeted Therapies of Advanced Basal Cell Carcinoma" by (Hoashi et al., 2022) provides a comprehensive overview of basal cell carcinoma (BCC), emphasizing its prevalence, characteristics, and the conditions under which it may metastasize. BCC is highlighted as the most common form of skin cancer, particularly among Caucasian populations, accounting for 80% to 90% of cases. The authors effectively establish the primary etiological factor of BCC as sunlight exposure, which underscores the importance of preventive measures against UV radiation.

The article delineates the generally indolent nature of BCC, noting that while metastasis is rare, certain clinical features can elevate the risk. Specifically, tumors located in the midline of the face or ear, those that have persisted for an extended duration, larger tumors, and a history of radiation exposure are identified as having a higher potential for metastasis. This classification is critical for clinicians as it aids in risk stratification and management decisions for patients presenting with BCC.

Moreover, the article addresses the uncommon but significant instances of BCC with intravascular invasion, which are associated with increased metastatic rates. This finding is particularly important as it suggests that even BCCs, typically regarded as low-risk tumors, can exhibit aggressive behavior under certain circumstances. The authors call for awareness among healthcare providers regarding these atypical presentations, which may necessitate systemic treatment approaches.

The discussion on treatment modalities for metastatic BCC is particularly relevant, as it highlights the need for systemic therapies in advanced cases. The article implies that early identification and intervention are crucial in managing BCC to prevent progression to metastatic stages. However, the authors could further elaborate on the specific systemic treatments available and their efficacy, which

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would provide a more rounded perspective on management strategies for metastatic BCC.

The article "Primary Basal Cell Carcinoma Masquerading as Metastatic Basal Cell Carcinoma in the Left Axilla" by (Haskell Hanisch et al., 2023) provides critical insights into the complexities surrounding the diagnosis and treatment of basal cell carcinoma (BCC), particularly in cases where the presentation may mimic metastatic disease. BCC, recognized as the most prevalent skin cancer, typically arises from the basal layer of the epidermis and is characterized by its shiny, pink papule or nodule appearance. The authors emphasize the importance of histological confirmation through biopsy in all suspected cases, which is vital for accurate diagnosis and treatment planning.

A significant focus of the article is the differentiation between primary BCC and metastatic BCC (mBCC), particularly in atypical presentations. The authors note that while mBCC is rare, it can occur, especially in cases of aggressive histopathologic variants. This underscores the necessity for clinicians to maintain a high index of suspicion and to conduct thorough evaluations when faced with unusual presentations of skin lesions.

The article also discusses the treatment modalities for BCC, highlighting that surgical intervention, particularly wide excision or Mohs surgery, remains the gold standard. The authors point out that radiation therapy is typically reserved for patients who are not surgical candidates or for tumors deemed inoperable, thus providing a comprehensive overview of treatment strategies. Furthermore, the discussion on environmental risk factors, such as UV exposure and skin type, serves to contextualize the epidemiology of BCC, with a noted increase in incidence correlating with age and prior history of non-melanoma skin cancer.

The introduction of hedgehog pathway inhibitors represents a significant advancement in the management of mBCC, allowing for targeted therapy in cases where traditional surgical options are not viable. This development reflects the ongoing evolution of treatment strategies in response to the challenges posed by aggressive forms of BCC.

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CONCLUSION

The literature on metastatic basal cell carcinoma (mBCC) reveals the rarity of this condition, which emerges from the more prevalent basal cell carcinoma (BCC), accounting for about 80% of nonmelanoma skin cancers. The studies reviewed indicate that mBCC typically arises from primary tumors in the head and neck region, predominantly affecting middle-aged men with a history of long-standing BCC ((S. Mehta et al., 2012); (Aditya & Rattan, 2013)). The incidence of metastasis is notably low, ranging from 0.0028% to 0.55%, necessitating careful monitoring for high-risk patients ((S. Mehta et al., 2012); (Piva de Freitas et al., 2017)).

Risk factors for mBCC include age, skin type, prior skin damage, and tumor characteristics, which significantly influence prognosis ((Aditya & Rattan, 2013); (Lance Cowey, 2013)). Once metastasized, BCC is associated with a poor prognosis, with surgical options often becoming limited as the disease progresses ((Lance Cowey, 2013)). The emergence of targeted therapies, particularly vismodegib, which inhibits the Hedgehog signaling pathway, marks a significant advancement in treatment options for advanced and metastatic cases ((Berrada et al., 2014); (Hoashi et al., 2022)). These therapies provide alternatives for patients unsuitable for surgery and represent a shift towards more personalized treatment approaches ((Lance Cowey, 2013)).

The literature also emphasizes the importance of accurate diagnosis, particularly in atypical presentations where primary BCC may mimic metastatic disease ((Haskell Hanisch et al., 2023)). Histopathological evaluation remains crucial in differentiating between these forms, as misdiagnosis can lead to inappropriate treatment strategies ((Haskell Hanisch et al., 2023)).

In conclusion, the body of literature on mBCC highlights its rarity and the complexities involved in its diagnosis and treatment. The low incidence of metastasis, coupled with the challenges posed by advanced forms of BCC, underscores the necessity for ongoing research into effective treatment modalities and the development of targeted therapies. Furthermore, understanding the risk

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factors and clinical characteristics associated with mBCC is essential for improving patient outcomes and guiding clinical management.

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