Basal cell carcinoma (BCC) is the most common malignancy arising from the epidermis, affecting approximately 1 million Americans per year [1]. It is known to be locally aggressive and metastasizes in only 0.03% of cases [2]. A 2016 literature review of metastatic basal cell carcinoma (mBCC) by Tang et al., reported an incidence of 0.0028% of mBCC and fewer than 300 reported cases in the literature, with the most commonly metastasizing lesions originating in the head and neck [3]. Additionally, the most common sites of metastasis are lymph nodes, lungs, bone, and abdominal organs respectively; with approximately half metastasizing to lymph nodes as the initial site of metastasis [3-5]. Furthermore, although less common, there have been cases in the literature, with the most commonly metastasizing lesions of bone marrow, spleen, liver, adrenal glands, brain, dura mater, esophagus, heart, and kidney [1]. Notably, bone was found to be involved in 20-30% of mBCC cases [2].

Our knowledge and understanding of molecular alterations in various cancerous events is progressively enriching. This exciting new acquired knowledge is developing into a major tool in management of various types of cancer. More understanding of mBCC is challenging and is needed to be able to manage the marked variability of the presentation of these tumors. With further understanding, especially the molecular alterations in BCC in general, we may even be able to develop a newer classification of these tumors with purpose of providing the optimal patient’s disease outcome.

**Case Presentation**

The patient is an 88-year-old man with a history of BCC of the skin of his right breast, which eventually lead to death due to wide metastatic disease. We describe the features of these tumors including diagnosis, molecular alterations, and management. In this report, we present a case of an 88-year-old man with history of BCC of the skin of his right breast, which eventually lead to death due to wide metastatic disease. We describe the features associated with the risk of metastasis and provide a brief review of the current literature.
IHC studies were performed on sections from the prior original tumor from the breast skin and the studies were similar to the studies on the current metastatic tumor. Additional IHC studies were also performed included negative for CEA, EMA, BCL-2 and E-Cadherin.

Although the patient had two malignancies, there was no family history of hereditary diseases or any abnormal genetic testing.

The patient was treated with systemic and local chemotherapy in addition to external beam radiation to alleviate the pain. He was disease-free for 11 months, after which he expired as a result of widespread metastatic disease.

Discussion

The first case of mBCC was reported in 1894 by Beadles [6]. In 1951, Lattes and Kessler described the criteria for diagnosis of mBCC: (1) the metastasis cannot be primarily squamous in origin [2,3], (2) sites of metastasis should be confirmed as thus, and not simply an extension of the original tumor or be a new primary growth in itself, and (3) cannot be of salivary or glandular origin [7].

Recorded cases show that mBCC occurred more often in men and tend to involve long-standing lesions that were neglected; refractory to treatment; metatypical, morphea form, or giant BCC in type; and arising from an index lesion in the head or neck [2,3,8]. Additionally, the presence of comorbidities was linked to higher morbidity in patients with dermatologic malignancy over the age of 80 [9]. The highest metastatic potential was seen in high-grade lesions with perineural invasion [4]. It is worthy to note, however, that mBCC does not seem to arise as a consequence of immunosuppression [4]. Robinson et al., summarized prior reported factors associated with metastasis and aggressive growth of basal cell carcinoma. In such aggressive tumors, they reported that Bcl-2 protein level is usually decreased; E-cadherin expression is usually decreased and may be associated with tumor invasion, increased desmoplastic tumor stromal response, and presence of basosquamous component among others [10].

Our reported case displayed various features of the reported aggressive and metastatic basal cell carcinoma, which in addition to age above 80 and vascular/perineural invasion, resulted in the unfavorable outcome and eventual death.

By now, it is clearly understandable that the identification of tumor-specific genetic alterations is currently one of the most active areas of molecular pathology research studies, and is having a major impact on the development of novel therapies targeting known abnormal signaling pathways. Recent advances...
in sequencing technology allowed genome-scale approaches to mutation discovery, identifying new genes and pathways potentially involved in BCC carcinogenesis.

Pellegrini et al., reviewed established knowledge and new hypotheses regarding the molecular genetics of BCC pathogenesis. It is established knowledge that several tumor suppressor genes and proto-oncogenes have been implicated in BCC pathogenesis, including the key components of the Hedgehog pathway, PTCH1 and SMO, the TP53 tumor suppressor, and members of the RAS proto-oncogene family. They concluded that a more complex genetic network of cancer-associated genes than previously hypothesized is involved in BCC carcinogenesis, with a potential impact on the development of new molecular targeted therapies [11].

A 2018 study by Kim et al. outlined the most recent treatment recommendations for mBCC, dividing patients into those with (1) regional lymph node metastasis and (2) those with distant metastatic spread. It is recommended that patients with local lymph node metastasis be treated aggressively with surgery, and if necessary, adjuvant radiotherapy [12,3].

In patients with distant spread, Kim et al. emphasized the importance of a multidisciplinary approach when considering treatment options, including sonic hedgehog inhibitors [12]. In 2012 the Food and Drug Administration approved a sonic hedgehog inhibitor, vismodegib, for the treatment of mBCC [13]. In a study by Yin et al., vismodegib showed a 50% response rate for locally advanced BCC or mBCC [14], and Pabst et al. noted that treatment with vismodegib demonstrated partial remission of a bony BCC metastasis [15]. Given that approximately 90% of BCC expressed abnormal hedgehog signaling [16], this appears to be a promising treatment.

If sonic hedgehog inhibitors are not feasible, Kim et al., suggested the consideration of platinum-based chemotherapy [12]. Additionally, a study by Cannon et al. demonstrated the successful treatment of mBCC with PD-1 inhibitors to lung metastasis but subsequent resistance to the drug in bony metastasis [17]. The authors remarked however that PD-1 inhibitors are often used as salvage therapy if standard treatment options prove to be insufficient [17]. Furthermore, Kim et al., noted the importance of palliative care to improve quality of life and patient comfort [12]. We do note that many of these papers express that the majority of data come from men, so the generalizability of these findings should be carefully considered.

It is important for pathologists to recognize mBCC as it carries a poor prognosis; the 5-year survival rate is approximately 10% [2]. Furthermore, patients with distant spread survive for approximately 10-14 months following confirmation of metastasis, with particularly poor prognosis of metastasis to the lungs, bone, or liver [2]. It is our hope that this report raises awareness of what remains an unmet need in diagnosis, molecular changes, and treatment of mBCC, and that continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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References