Basal Cell Carcinoma With Pulmonary and Lymph Node Metastasis Causing Death

June K. Robinson, MD; Madhu Dahiya, MD

Background: The incidence of metastatic basal cell carcinoma ranges from 0.003% to 0.55%. The 230 reported cases most often occurred in long-standing recurrent lesions and appeared in regional nodes or the lungs.

Observations: The stromal dependence of the tumor provides an explanation for the nonmetastasizing nature of basal cell carcinoma. The dense fibrous stroma of the lymph node in the case of metastatic basal cell carcinoma reported in the present study is similar to other reported cases with metastases to lymph nodes, bone, bone marrow, glands, and subcutaneous tissue.

Conclusions: This metastatic basal cell carcinoma demonstrated lymphatic and hematogenous dissemination to the lungs and lymph nodes. A dense accumulation of microvessels was present at the boundary of the tumor nests and dermal stroma and in the stroma surrounding the tumor in the lymph node.

Arch Dermatol. 2003;139:643-648

REPORT OF A CASE

A 55-year-old man presented for Mohs surgical resection of a BCC of the right posterior upper shoulder in 1984 that recurred after 2 previous treatments. The tumor was initially treated with electrodesiccation and curettage in 1980, and the recurrence was excised in 1982. He presented for care with a 3.2×3.8-cm scar on the right posterior shoulder having clinically apparent recurrent BCC in the lateral part of the scar (Figure 1A). The Mohs surgical resection of this T3 tumor was 24.6 cm² (diameter of resection, 6.0×4.1 cm) and extended into the muscle. The infiltrating BCC penetrated the fascia and extended between the muscle bundles (Figure 1B). Perineural spread was not seen; however, BCC was present within the lumen of an artery within the muscle (Figure 2). Complete blood count and findings from liver function tests, chest radiography, bone scan, and computed tomography of the chest, brain, and abdomen were normal. Five years after surgery, in 1989, there was no recurrence at the site of the resection on the shoulder, but the patient developed a 1.6-cm, firm, palpable right axillary node. Complete blood count and findings from liver function tests, chest radiography, bone scan, and computed tomography of the chest, brain, and abdomen were normal. Axillary lymph node dissection was positive for MBCC in 2 of 5 nodes. The histologic pattern re-
sembled that of the tumor of the skin of the right shoulder with infiltrating BCC with fibrous stroma.

During the node dissection, the tumor was adherent to the axillary vein and could not be resected. The axilla was treated with 4500 rad (45 Gy) of local radiation, and the area of tumor adherent to the axillary vein received a total of 6600 rad (66 Gy) over 3 months.

This right-handed man developed severe lymphedema of the right arm. In spite of daily treatment with a 10-chamber compression pump (Lymphapress; Mego-Afek, Kibbutz Afek, Israel) and a Jobst garment, the use of his hand was severely limited. In 1994, radionecrosis of the axillary vault caused acute arterial bleeding, which was repaired with an arterial graft. There was constant lymphatic axillary drainage, which required packing with absorbent material. He died in 1997, 8 years after the axillary dissection, from hemorrhaging into pulmonary metastases.

**METHODS**

**HISTOLOGIC ANALYSIS**

Surgical samples of the lymph node were fixed in 10% formalin and embedded in paraffin. Selected Mohs surgical specimens were also fixed in formalin and embedded in paraffin. Paraffin embedded 3-µm sections were cut and stained with hematoxylin-eosin. Infiltrating BCC was surrounded by dense stroma in lymph node and the dermis.
IMMUNOHISTOCHEMICAL ANALYSIS

Immunohistochemical staining was performed on deparaffinized tissue sections cut at 5 µm by the Ventana automated method. The following mouse antibodies were used: CEA (Ventana, Tuscon, Ariz), CK-pan (Ventana), EMA (Ventana), Bcl-2 (Ventana), CK-7 (Ventana), CD31 (Ventana), CD34 (Ventana), and Ber Ep4 (Biocare Medical, Walnut Creek, Calif).

Tumor specimens from the recurrent tumor in the skin and from the MBCC in the axillary lymph node were examined with a serial immunopanel (CEA, CK-pan, EMA, Bcl-2, CK-7, and Ber Ep4) to determine the cell of origin of the tumor and demarcate the endothelial cells (CD31 and CD34) forming the microvasculature (Table 1). The intense Ber Ep4 expression by tumor cells supports a diagnosis of BCC; the negative staining for EMA argues against a basosquamous cell carcinoma. Similarly, the negative CEA and very weak focal cytokeratin 7 expression, combined with the characteristic histologic features of the tumor nests, argues against a metastatic breast or lung carcinoma. The CD31 and CD34 highlights the pattern of microvasculature hugging the interface of the tumor nests and the stroma in both specimens (Figure 3B and C). Occasional microvessels were apparent within the tumor nests.

**MBCC REPORTED IN THE LITERATURE**

Most of the 230 reported cases of MBCC during the period 1894 to 2000 were identified in the last 30 years. A total of 140 cases provided a photomicrograph or described the stroma of the primary tumor and the stroma in the lymph node metastasis; 42 cases described the stroma in the visceral metastasis as mucinous fibrous tissue surrounding the islands of BCC. The fibrotic stroma surrounding the MBCC was described as dense (lymph node, bone, bone marrow, or salivary and parotid glands) sparse (lung or liver), or not present (adrenal gland, spleen, or brain).

**COMMENT**

The incidence of MBCC ranges from 0.01% in pathologic specimens through 0.03% in dermatology patients to 0.1% in data from surgical centers. Variation in the reported incidence may be due to selection bias from the sources of the data and exclusion of BCC from

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**Table 1. Immunohistochemical Expression by the Tumor**

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Recurrent Skin Tumor</th>
<th>Metastatic Tumor in Lymph Node</th>
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<tbody>
<tr>
<td>CEA</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CK-Pan</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>EMA</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>+ Focal weak</td>
<td>+ Focal weak</td>
</tr>
<tr>
<td>CK-7</td>
<td>+ Focal weak</td>
<td>+ Focal weak</td>
</tr>
<tr>
<td>Ber Ep4</td>
<td>+</td>
<td>+ Stromal microvessels</td>
</tr>
<tr>
<td>CD31</td>
<td>+ Stromal microvessels</td>
<td>+ Stromal microvessels</td>
</tr>
<tr>
<td>CD34</td>
<td>+ Stromal microvessels</td>
<td>+ Stromal microvessels</td>
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Abbreviations: +, positive; −, negative.

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**Figure 3.** A, Infiltrating basal cell carcinoma surrounded by dense stroma in lymph node (hematoxylin-eosin, original magnification ×10). B and C, The CD34 delineates microvessels cuffing the dermal interface of the tumor nests (B) and microvessels within tumor nests (C) in the metastatic basal cell carcinoma in the lymph node (CD34 immunoperoxidase, original magnification ×20).

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traditional cancer registries in the United States. In the Danish registry, the estimated lethality of BCC is 0.12%, which may be inferred to be principally from MBCC and local infiltrative growth into vital structures. The criteria for the 230 reported MBCC cases were that the primary tumor is from skin and not mucous membranes or glandular or other origin; metastasis occurred in a site distant from the primary tumor and cannot be a result of direct extension, and both metastatic and primary lesions must have similar histologic subtypes.

While the usual MBCC is a large, ulcerated, locally invasive BCC of the head and neck that recurs despite repeated surgical procedures or radiotherapy, these features are not absolute prerequisites for metastasis. Immunosuppression does not appear to be a cause of MBCC. In one review of 170 cases, the median interval between onset of BCC and metastasis was 9 years, with a range of less than 1 year to 45 years. Despite the long period from onset to metastasis, the tumor behaves aggressively once metastasis occurs. In the same review, 8 months after the first symptoms of metastasis, half of the patients were deceased. Our case had a 9-year period from onset of the BCC to metastasis, and the patient survived for an additional 8 years from discovery of the lymph node metastasis until his death.

While some believe that metatypical or basosquamous-type BCC is the most likely to metastasize, most report no specific histologic type of BCC as more capable of metastasizing. Perineural spread and invasion of blood vessels by BCC (Figure 2) enhance the likelihood of metastasis. Vascular lumina large enough to transmit tumor emboli are commonly located at or deep to the fascia over the muscle. While BCC invades blood vessels and may be present intraluminally, the tumor cells may not survive the physical changes induced by circulation to remain viable and implant in a capillary bed. In addition, immunologic surveillance may impair tumor growth at a distant site.

Metastasis may depend on the size of the original tumor and the depth of tumor invasion. Tumors greater than 3 cm in diameter have a 2% incidence of metastasis and/or death. This increases to 25% in those lesions more than 5 cm in diameter and to 50% in lesions more than 10 cm in diameter. Primary tumors invaded deeply into extradermal structures, such as cartilage, skeletal muscle, or bone. There were only 2 case reports of BCC smaller than 1 cm in diameter leading to metastasis.

About half of MBCC have metastasis to lymph nodes as the first site, but the hematogenous route to lungs and bones is also equally represented. Metastases to liver, other viscera, and subcutaneous tissues may occur, but these areas were usually involved when lymph nodes, lungs, or bones were also affected. Once distant spread occurs, response to chemotherapy with methotrexate, fluorouracil, bleomycin, and cisplatin is marginal, and survival rarely exceeds 1.5 years.

Basal cell carcinoma has a keratin pattern resembling the outer root sheath of the hair follicle below the isthmus and/or the bulge region of the vellus hair follicle, rather than that of the basal cell epithelium. This keratin pattern supports the follicular origin of BCC. The follicular origin of BCC may explain the stromal dependency of BCC noted in the 1960s. Stromal dependent tumor maturation is governed by the connective tissue in its proximity. Lyles et al in 1960 and Blackwell and McComb in 1969 performed autotransplantation of BCC in human volunteers with little to no success. In 1961, Van Scott and Reinertson also failed when transplanting only the epithelial parts of BCC, but when the stroma was included with the epithelial parts of BCC, some transplantations succeeded in human volunteers. Transplantation of BCC into the anterior chamber of the rabbit’s eye and the intrauterine cavity

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Table 2. Factors Associated With Metastasis and/or Aggressive Growth of Basal Cell Carcinoma

<table>
<thead>
<tr>
<th>Extrinsic to the Cell</th>
<th>Intrinsic to the Cell</th>
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<tbody>
<tr>
<td>Microvessel count</td>
<td>Cell cycle proteins</td>
</tr>
<tr>
<td>Aggressive BCC has greater microvessel density</td>
<td>Bcl-2 protein level is decreased in aggressive BCC</td>
</tr>
<tr>
<td>Stromal response</td>
<td>Metastatic BCC: no loss of Bcl-2 and CD44 expression</td>
</tr>
<tr>
<td>Increased presence of myofibroblastic markers and stromal fibroblastin and discontinuous basement membrane around aggressive BCC</td>
<td>No difference in Ki-67 between “horrifying” and “nonhorrifying” BCC</td>
</tr>
<tr>
<td>Higher expression of TIMP-2 mRNA in BCC (matrix metalloproteinase inhibitor) may be related to decreased metastatic potential</td>
<td>Tumor cell type</td>
</tr>
<tr>
<td>Reduced level of basement membrane antigens in BCC and decreased collagen production at tumor edge in BCC</td>
<td>“Basosquamous” carcinomas may behave more aggressively</td>
</tr>
<tr>
<td>Perineural invasion related to aggressive BCC</td>
<td>BerEp4 is expressed in BCC and EMA is expressed in SCC, both immunostain “basosquamous” cell carcinoma</td>
</tr>
</tbody>
</table>

Abbreviations: BCC, basal cell carcinoma; mRNA, messenger RNA; SCC, squamous cell carcinoma; TIMP-2, tissue inhibitor of metalloproteinase.
of the rat was unsuccessful.\textsuperscript{34,35} It is believed that failure of BCC to grow in tissue culture may be related to its stromal dependence. Grimwood and colleagues' successful transplantation of human BCC with its stroma into nude mice reinforces the stromal dependency of BCC.\textsuperscript{36}

Given the probable follicular origin of BCC, surgical experience with hair transplantation provides a model for survival of metastatic cells at distant locations. Single follicular units are transplanted with success when a portion of the stroma is also transplanted; however, overly aggressive trimming of tissue around the follicle results in their loss.\textsuperscript{37} The stromal dependency of BCC implies that embolic, potentially metastatic cells either carry their stroma with them to survive and proliferate or evolve a biological mechanism to support independent stromal proliferation in the new location. Dense fibrous stroma characterizes metastatic lesions of the bone, bone marrow, salivary and parotid glands, subcutaneous tissue, and especially those in lymph nodes, the most common site of metastasis (Figure 3A). However, the stroma of MBCC to the lung and liver, which are sites of hematogenous dissemination, is sparse.

Recent studies in melanoma, invasive breast cancer, non–small cell lung carcinoma, invasive prostate carcinoma, and head and neck squamous cell carcinoma have suggested that tumor angiogenesis (expressed as the microvessel density within the tumor and in areas adjacent to the tumor-stroma interface) significantly correlates with tumor aggressiveness and the overall survival of patients with solid tumors.\textsuperscript{38-45} Tumor growth and metastasis are dependent on tumor neovascularization. Tumors may persist as asymptomatic lesions, but only vascularized tumors may grow rapidly and expand locally or metastasize.\textsuperscript{39,40}

Staibano et al.\textsuperscript{47} found that microvessel density is greater in the stroma of biologically aggressive BCC. In addition to the stromal influences, which are extrinsic to the cell, BCC may provide signals (intrinsic to the cell) to the stroma to transform fibroblasts at the borders of tumor nests into microvessels, which support tumor growth.\textsuperscript{17-67} (Table 2). In this case of metastatic BCC, microvessels defined by CD34 are particularly evident at the boundary of the tumor and stroma, at the invasive front of the lesion, and between thin sheets of invasive cells, even at a considerable distance from the principal tumor mass in the lymph node, which supports the theory that the tumor influences the stroma to produce the microvessels (Figure 3B and C). In theory, potentially metastatic cells either carry their stroma with them to survive and proliferate or evolve a biological mechanism to support independent stromal proliferation in the new location. This case of BCC metastatic to axillary lymph nodes illustrates that metastatic cells take stroma with the cells to proliferate and the pulmonary metastasis may represent the evolution of a mechanism to support independent stromal proliferation by intrinsic cell signals. Understanding the mechanisms of tumor growth by extrinsic and intrinsic signals may provide new therapeutic avenues.

Accepted for publication September 10, 2002.

This study was supported in part by Division of Dermatology and Department of Pathology funds, Loyola University Stritch School of Medicine.

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