Conventional Versus Giant Basal Cell Carcinoma, a Review of 57 Cases: Histologic Differences Contributing to Excessive Growth

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Abstract

Background: Giant basal cell carcinoma (GBCC) is defined as a basal cell carcinoma (BCC) exceeding 5 cm in size. While these tumors impart significant morbidity due to local tissue destruction and have a higher rate of metastatic disease than their conventional (smaller) counterparts, reasons for their large size remain unclear. While theories relating to neglect or faster growth rate are often invoked; to date, there has not been a comprehensive evaluation of the histologic features of these large tumors that may contribute to their size. Methods: Histologic features of GBCCs (n = 29) were evaluated and compared to those of conventional BCC (n = 28). Available clinical demographic data were also reviewed. Results: GBCCs, in addition to overall larger size, more often were thicker, displayed ulceration, and showed a more infiltrative growth pattern than their conventional counterparts. These rare tumors also displayed an insignificant increased propensity for a brisk host immune response, and the infiltrate significantly more often included clusters of plasma cells. Conclusions: Most histologic features seen in GBCCs likely reflect their large size. Histologic features alone are unlikely to explain the size of these rare tumors. The possibility of an altered host immune response contributing to the growth of these tumors requires further investigation.

Key Words: Basal cell carcinoma, giant basal cell carcinoma, host immune response, plasma cells

Introduction

The most common cutaneous malignancy seen around the world in fair-complected populations is basal cell carcinoma (BCC), outnumbering squamous cell carcinoma by 4:1.[1-3] While they may be locally invasive and destructive, this tumor rarely metastasize and surgery most often is curative.[1] BCC is generally classified into subtypes determined by histopathologic growth pattern and designed to indicate their propensity for aggressive behavior. Superficial and nodular subtypes indicate relatively indolent behavior, while micronodular and infiltrative/morpheaform subtypes correspond to more locally aggressive behavior.[1,4-7] This study focuses on giant BCC (GBCC), which can comprise any of the above-mentioned histopathologic subtypes and is currently classified by size alone (>5 cm in greatest dimension).

While comprising <0.5% of all BCCs, morbidity imposed by GBCC can be substantial.[2,8] The cause for excessive growth in GBCC is unknown; existing theories invoke patient characteristics, characteristics of the tumor, or its microenvironment. Neglect, denial, and inability/unwillingness to seek treatment, weakened immunity, and oncogenic viruses have all been suggested as reasons for the large size of GBCC.[1,5,9-11] Some literatures suggest that larger BCC may grow at a faster rate than conventional BCC.[12,13] While studies examining the clinical characteristics of these rare tumors exist,[1,14] large case series specifically investigating the histopathologic features of GBCC are lacking in the current literature. It is unknown whether GBCCs possess unique histological features that could contribute to their large size and potentially faster growth rate. We hypothesized that GBCC may possess unique histopathologic characteristics compared to conventional

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BCC that could explain their large size, and we evaluated histopathologic characteristics of these tumors.

Materials and Methods

After Institutional Review Board approval, histology slides and blocks were retrieved from the pathology department of our institution in the central United States and from a local private dermatopathology practice. GBCCs were identified by searching pathology reports where either (1) clinical tumor size was mentioned in accompanying clinical information or corresponding clinical note in the electronic medical record or (2) gross description and/or final diagnosis described tumor size >5.0 cm. In total, 29 GBCCs were retrieved, both biopsies and excisions. A control group of samples (n = 28) comprised of a similar number of biopsies and excisions, based on the evaluation of surgical pathology reports documenting tumor size (within clinical information, gross description, or final diagnosis) as <5.0 cm. Recurrent tumors were excluded. For both groups, if the case consisted of multiple blocks with tumor, all slides from the case were blindly reviewed by one pathologist (S. C. S.), but a representative slide documenting the deepest area of invasion was chosen for inclusion in the study and reviewed by all study authors. Once retrieved, the slides were randomized. Appropriate demographic data were recorded from pathology reports including patient sex, age, tumor site, and size. Duration of tumor growth was generally not included on reviewed pathology reports, and our study was not designed to collect this information from the clinical records. Similarly, Fitzpatrick skin type was generally not included on reviewed pathology reports; however, as this study was conducted in the central United States, it can be safely presumed that the majority (if not all) of the patients in this study were fair-skinned Caucasians. All authors (including board-certified dermatopathologists S. C. S. J. M. G., and J. A. B.) examined and recorded histopathologic characteristics of each tumor blinded to tumor size. The following characteristics were recorded: subtype (nodular, infiltrative, or superficial), tumor thickness/depth of invasion, perineural or lymphovascular invasion, host inflammation components, mitoses per mm², necrosis, significant squamous or adnexal differentiation, tumor cell pleomorphism, calcification, and ulceration. Any other concurrent diagnoses were also noted. Tumor thickness/depth of invasion was measured as for melanoma, assessed in millimeters by measuring from granular layer of the epidermis to the deepest extent of dermal involvement by tumor. When granular layer was not present due to ulceration, measurement was made from the base of the ulcer to the deepest extent of dermal involvement. Host inflammation was graded as low (absent, minimal, or nonbrisk) and high (brisk infiltrate consistently associated with majority of tumor nests). Presence or absence of plasma cell (PC) aggregates was also recorded. Results were recorded, analyzed, and statistical analyses were applied when appropriate. All statistics and calculations were performed using automated calculations for Fisher’s exact test, Chi-square test, and Student’s t-test, provided by GraphPad software (http://graphpad.com/quickcalcs, GraphPad Software, La Jolla, CA, USA).

Results

A total of 57 patient samples were obtained for analysis in this study, comprising 28 conventional BCCs and 29 GBCCs. Gender distribution in the conventional BCC group was 28.6% females (8/28) and 71.4% males (20/28), while proportions in the GBCC group were 17.2% females (5/29) and 82.7% males (24/29) (P = 0.36). Ages of patients diagnosed with BCC ranged from 40 to 87 years, with a mean of 66.5 ± 17.76 years, similar to ages of patients in the GBCC group, which ranged from 28 to 89 years, with a mean of 66.9 ± 15.74 years (P = 0.90). Specimen types (biopsies and excisions) were equally represented in both groups, with biopsies representing 13/28 and 13/29 of BCC and GBCC groups, respectively (P = 1.0). Anatomic site of tumors was also similar between groups. In the conventional BCC group, 60.7% of tumors (17/28) were located on the head and neck, 25% (7/28) on the trunk, and 14.3% (4/28) on the extremities. Similarly, in the GBCC group, 55.2% of tumors (16/29) were located on the head and neck, 27.6% (8/29) on the trunk, and 17.2% (5/29) on the extremities. Demographic information for the two groups is provided in Table 1.

Histologic features of the tumors are recorded in Table 2. As expected, average tumor size, as determined by the greatest single dimension recorded, differed significantly between groups: average size of GBCC was 6.96 cm and was 1.54 cm for conventional BCC (P < 0.001). Average

| Table 1: Clinical and demographic information of giant versus conventional basal cell carcinoma |
|---------------------------------|-----|-----|-----|
| **Sex**                         |     |     |     |
| Female                          | 5   | 8   | 0.36 | NS  |
| Male                            | 24  | 20  |      |     |
| Age, year (average)             | 66.9| 66.5| 0.89 | NS  |
| Range                           | 28-89| 40-87|      |     |
| **Specimen type**               |     |     |     |
| Excision                        | 16  | 15  | 1.00 | NS  |
| Biopsy                          | 13  | 13  |      |     |
| **Anatomic site**               |     |     |     |
| Head/neck                       | 16  | 17  |      |     |
| Trunk                           | 8   | 7   |      |     |
| Extremity                       | 5   | 4   |      |     |

GBCC: Giant basal cell carcinoma, BCC: Basal cell carcinoma, NS: Not statistically significant.
depth of invasion was significantly greater in GBCC, with conventional BCC group ranging from 0.25 mm to 10 mm (average: 3.14 mm, standard deviation [SD]: 2.7 mm) but with GBCC group ranging from 0.35 mm to 23 mm (average: 5.83 mm, SD: 5.75) \( (P = 0.03) \). Ulceration was present significantly more often in GBCC, with 22 of 29 tumors (75.9%) displaying surface ulceration compared to 6 of 28 (21.4%) in conventional BCC \( (P < 0.0001) \). Admittedly, these statistical significances of depth and ulceration status may simply reflect the overall greater size of GBCC.

GBCCs more frequently displayed an aggressive subtype than conventional BCC [Figures 1 and 2]. Of conventional BCCs, 16 were classified as nonaggressive subtypes (nodular, superficial, or both nodular and superficial), while 12 tumors (43%) were classified as aggressive subtypes (infiltrative or nodular/infiltrative). In contrast, 7 GBCC tumors were classified as nonaggressive subtypes and 22 tumors were classified as aggressive subtypes (76%) \( (P = 0.016) \). Although necrosis was more often present in GBCC, seen in 68.9% of cases (20/29) versus 57.1% of conventional BCC (16/28), this trend was not statistically significant \( (P = 0.42) \) and likely simply reflects the greater size of GBCC.

Adnexal differentiation was completely absent in all cases of GBCC, while seven conventional BCCs (all nodular subtypes) showed evidence of adnexal differentiation [Figures 3 and 4], as evidenced by ductal, matrical, or trichilemmal differentiation \( (P = 0.0045) \). The frequency of squamous differentiation (squamatization) within tumor lobules was similar in GBCC \( (n = 20/29, 68.9\%) \) and conventional BCC \( (n = 20/28, 71.4\%) \) and was not significantly different between the groups \( (P = 1.00) \). Calcification was present in both tumor types at an approximately equal frequency (GBCC: \( n = 9/29, 31\% \), and conventional BCC: \( n = 10/28, 35.7\% \)); this feature was not statistically different between the groups \( (P = 0.71) \).

Lymphovascular invasion was not detected in any tumor. Perineural invasion was observed in 13.8% of GBCCs (4/29) and 10.7% (3/28) of conventional BCCs \( (P = 0.72) \). All cases exhibiting perineural invasion (excluding one case) were of the infiltrative subtype [Figure 5]. Although mitotic rate trended higher in GBCC \( \text{average: } 18.6/\text{mm}^2, \text{SD: } 12.66, \text{and range: } 2–67 \) compared to conventional BCC \( \text{average: } 15/\text{mm}^2, \text{SD: } 10.75, \text{and range: } 0–34 \), this parameter was not statistically significant \( (P = 0.25) \).

Tumor cell pleomorphism [Figure 6] was observed more frequently in GBCC \( (n = 6, 20.6\%) \) than in conventional BCC \( (n = 2, 7.1\%) \), although this parameter was not statistically significant \( (P = 0.25) \).

Host response to tumor was also evaluated. The host response in each tumor was classified as absent, minimal, nonbrisk, or brisk. Absent, minimal, and nonbrisk inflammations were grouped together into a “low inflammation” category, which was compared to the incidence of brisk (high) inflammation. GBCCs tended to have high inflammation more often than did conventional BCCs, but this difference was not

| Table 2: Histopathologic features of giant versus conventional basal cell carcinoma |
|-------------------------------|-----------------|--------|----------|-----------------|
|                              | GBCC            | BCC    |      \( P \)      | Significance |
| Average size (cm)            | 6.955           | 1.544  | \( <0.001 \)      | S            |
| Morphologic subtype          |                 |        |                  |               |
| Aggressive*                  | 22              | 12     | 0.02        | S            |
| Nonaggressive**              | 7               | 16     |              |              |
| Depth of invasion (mm)       | 5.83            | 3.14   | 0.03        | S            |
| Ulceration                   | 22              | 6      | \( <0.0001 \)   | S            |
| Mitotic rate (/mm\(^2\))     | 18.6            | 15     | 0.25        | NS           |
| Inflammatory pattern         |                 |        |                  |               |
| Brisk (high)                 | 8               | 4      | 0.33        | NS           |
| Nonbrisk/minimal/absent (low)| 21              | 24     |              |              |
| Invasion                      |                 |        |                  |               |
| Perineural                   | 4               | 3      | 0.72        | NS           |
| Lymphovascular               | 0               | 0      |              |              |
| Differentiation              |                 |        |                  |               |
| Squamous                     | 20              | 20     | 1.00        | NS           |
| Adnexal                      | 0               | 7      | 0.005       | S            |
| Pleomorphism                 | 6               | 2      | 0.25        | NS           |
| Calcifications present       | 9               | 10     | 0.71        | NS           |
| Necrosis                     | 20              | 16     | 0.42        | NS           |
| Plasma cell aggregates       |                 |        |                  |               |
| Present                      | 28              | 16     | 0.0004      | S            |
| Absent                       | 1               | 12     |              |              |

*Aggressive includes: Infiltrative, nodular/infiltrative, **Nonaggressive includes: Nodular, superficial, superficial/nodular. S: Statistically significant, NS: Not statistically significant, GBCC: Giant basal cell carcinoma, BCC: Basal cell carcinoma.
statistically significant ($P = 0.3313$). Interestingly, PC aggregates in association with the tumor (defined as >5 PCs clustered together in proximity to the tumor) were found to be significantly more common in GBCCs [Figures 7 and 8] than conventional BCCs. Twenty-eight of 29 GBCCs displayed PC clusters (96.55%) compared to 16 of 28 conventional BCCs (57.14%) ($P = 0.0004$).

**Discussion**

BCC is derived from its putative cell of origin, the basal cell, a type of keratinocyte located in the basal layer of the epidermis\(^\text{[14]}\) and responsible for dividing and replenishing keratinocytes of the epidermis.\(^\text{[1,15]}\) However, many experts now regard the tumor to have its origin in follicular epithelium.\(^\text{[16]}\) Like most skin cancers, ultraviolet (UV) light plays an important role in the development of BCC. In this case by disrupting the Hedgehog signaling pathway.\(^\text{[17]}\) Derangement of this pathway results in unregulated cell proliferation that culminates as a cutaneous malignancy.\(^\text{[17]}\) Up to 85% of BCCs will contain mutations with genes involved in Hedgehog signaling, most commonly patched (PTCH) and smoothened (SMO).\(^\text{[18]}\) While UV light may induce somatic mutations in these genes and contribute to tumorigenesis, inherited mutations also play a role in tumor susceptibility. PTCH mutations are commonly found in patients with basal cell nevus (Gorlin) syndrome. Recent studies have also focused on examining other putative genetic and epigenetic alterations that would predispose certain individuals to the development of BCC. Single-nucleotide polymorphisms in a variety of genes have been shown to occur more frequently in patients diagnosed with BCC, including genes encoding proteins involved in DNA mismatch repair,\(^\text{[19–21]}\) telomere biology,\(^\text{[22,23]}\) immune regulation,\(^\text{[22]}\) tumor progression,\(^\text{[22]}\) and skin pigmentation.\(^\text{[22,24]}\)

GBCC, first recognized in 1951 by Eckhoff, is defined as a subtype of BCC that exceeds 5 cm in diameter. The largest series regarding GBCC to date is a 2009 meta-analysis...
and basic histologic parameters (size and subtype). The largest series to date documenting histopathologic features of these unusual neoplasms is a recent case–control study of 13 GBCCs, which also examined the expression of neuromediators by immunohistochemistry as a mechanism to explain their large size. Most previous reports note that GBCCs commonly occur on the trunk as compared to conventional BCCs’ predilection for the head/neck region. Our study did not corroborate this anatomic site distinction. In our series, similar to the recent study by Yazdani Abyaneh et al., GBCCs were seen with the highest incidence in the head/neck region, similar in incidence to conventional BCCs. This difference may reflect that ours is a retrospective study based on pathology reports from the archives predominantly from an academic hospital rather than a prospective, clinically oriented study. Our case material may be biased toward complicated surgical cases and could inadvertently exclude cases which were treated by other modalities.

The histological subtype of the tumor is said to play an important role in the development of GBCC, with some subtypes (infiltrative/morpheaform, micronodular, and basosquamous (previously metatypical)) being associated with a more aggressive course. Regardless of subtype, all GBCCs are capable of deep invasion with penetration into muscle or bone. Prior studies indicate that the majority of GBCC have an aggressive histologic subtype. Indeed, the majority of GBCC in our series had an infiltrative subtype, either alone or with a nodular component, supporting the findings of those previous studies. The infiltrative growth pattern was significantly more common than in conventional BCC, of which a minority showed infiltrative subtype.

Despite the fact that GBCC rarely metastasizes, the extent of local destruction represents a significant clinical management issue and often extensive morbidity for the patient. Surgical treatment may be a challenging endeavor in the head/neck region where many of these tumors arise. Vismodegib and more recently sonidegib, the Food and Drug Administration-approved sonic Hedgehog pathway inhibitors for unresectable or metastatic BCC, may be used to induce regression or shrink the tumor to a resectable size. Mohs microsurgery may be appropriate in cases where tissue sparing is imperative. Metastasis in GBCC has been reported, with bone marrow involvement leading to myelophthisic anemia; vismodegib would be the first-line therapy in cases of metastatic GBCC.

The cause for excessive growth in GBCCs is unknown. While genetic predispositions exist for the development of BCC of any type, no study to date has identified reproducible genetic susceptibility to the development of GBCC, likely due to the rarity of this tumor. The most widely accepted hypothesis suggests that GBCC

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Figure 6: Tumor cell pleomorphism was detected in a subset of tumors, as seen in this example of a giant basal cell carcinoma. Tumor cell necrosis is also present (Case 46) (H and E, ×400)

Figure 7: Plasma cells were more commonly seen as part of the host response in giant basal cell carcinomas (Case 5) (H and E, ×200)

Figure 8: This giant basal cell carcinoma demonstrates large numbers of plasma cells, including some that have intracytoplasmic Russell bodies (immunoglobulin inclusions) (Case 30) (H and E, ×400)
is simply a product of neglect and allowed a longer clinical time course to reach maximum size, often over a period of 10–20 years. Support for this theory stems from an observation that this tumor is most commonly diagnosed in patients with lower socioeconomic status or physical disability, patient characteristics that may lead to delay in diagnosis and seeking treatment.\textsuperscript{10,11,13} Of note, in our study, we found that the average age of diagnosis of GBCC was similar to the age of diagnosis of conventional BCC. This series was designed only to examine the histologic parameters of GBCC and our data collection did not include information from the clinical records such as the duration of tumor growth prior to presentation for medical care. Therefore, while our observation regarding the age of presentation does not exclude a role for neglect in these large tumors, it also does not support the notion that patients with GBCC are simply waiting longer to present to a physician.

Other theories for the large size of GBCC exist. Northington \textit{et al.} suggest that anogenital human papillomavirus (HPV) subtypes may be pathogenic in the development of some chronic GBCC, as those HPV subtypes have been isolated from these tumors in some studies.\textsuperscript{9} Yazdani Abyaneh \textit{et al.} suggested that differing neuromodulator expression could account for size difference, but found that the expression of adrenocorticotrophic hormone (ACTH), serotonin, \(\beta\)-endorphin, and met-enkephalin was similar in GBCC and conventional BCC.\textsuperscript{13} Other authors suggest that a weakened immune system plays an important role in tumorigenesis,\textsuperscript{1} and at least one study has found single-nucleotide polymorphisms in genes important in immune regulation in patients developing BCC (of any type, not specifically GBCC).\textsuperscript{22} Our study showed a nonsignificant trend toward more host inflammation in GBCC compared to conventional BCC; this finding would suggest that patients with GBCC can mount a host response, although our study was not designed to assess the functional capacity of the infiltrate. Local immune suppression may occur following chronic UV exposure, shifting predominant T-cell subsets in skin from a cytotoxic/effector phenotype to a regulatory phenotype, thereby promoting a microenvironment that is more suitable for tumor growth.\textsuperscript{32} BCC specifically has been shown in some studies to have a Th2-dominant host response with many T-regulatory cells already present.\textsuperscript{33} Cytotoxic T-cells within the peritumoral infiltrate are speculated to contribute to the restriction of tumor growth.\textsuperscript{14} Analysis of T-cell subsets within the host responses of GBCC and conventional BCC would be useful to more specifically characterize potential differences between the two different host immune microenvironments.

We observed a statistically significant increase in the presence of plasma cell (PC) aggregates within GBCC. PCs are infrequently commented upon in literature regarding cutaneous neoplasia and host responses. One study of 175 consecutive BCC found PC to be present in 65% of cases, with PC being more often seen in aggressive subtypes of BCC.\textsuperscript{35} PCs were also more often seen in ulcerated tumors and from male patients.\textsuperscript{36} both features of which were more common in our GBCC group. Whether PC aggregates indicate a yet undescribed role of humoral immunity in tumor microenvironment and host defense against BCC remains to be determined. However, a recent publication determined that melanomas with sheets or clusters of PCs had significantly worse survival than melanomas without PCs.\textsuperscript{34} Melanoma rich in PCs were seen statistically more often in older patients, ulcerated tumors, and tumors with high mitotic activity.\textsuperscript{34}

Innately difficult is determination of growth rate to assess whether GBCC grows more quickly than conventional BCC. Some literature suggests that larger tumors grow at a faster rate.\textsuperscript{12,13} In our study, GBCC was significantly deeper and more often ulcerated than its conventional counterpart, but these features may be accounted for simply by the greater size of GBCC rather than as a surrogate marker of rapid growth. Even their more frequent infiltrative subtype does not indicate a more rapid growth rate.

Our study identified several other notable, albeit nonsignificant, trends. Absolute data show that GBCC harbors a greater incidence of tumor cell atypia/pleomorphism (three times the rate of conventional BCC). Although histological grading is not routinely performed in BCC, high-grade cytologic atypia can influence prognosis in cancer of other organs. One study found nuclear pleomorphism predicted BCC recurrence in a univariate analysis,\textsuperscript{37} although this feature did not turn out to be an independent prognostic variable for recurrence upon multivariate analysis.\textsuperscript{38} Another interesting finding was absent adnexal differentiation in any of the 29 cases of GBCC, as opposed to 7 cases of conventional BCC that showed at least focal adnexal differentiation. Adnexal differentiation (including matrical, trichilemmal, or ductal) could correspond to a more “well-differentiated” tumor, a feature which, like nuclear grade, has prognostic meaning in cancer of other noncutaneous organs.

**Conclusions**

The conclusions drawn by our study are somewhat limited by its design. Clinical information such as physical status of patients, disease duration prior to diagnosis, and clinical course information such as prior administration of radiation or chemotherapy, recurrence, distant metastases, and mortality were not designed to be assessed by the current study. Addition of such information would be beneficial for a more complete analysis.
Although the process driving excessive growth displayed by GBCC is likely not entirely evaluable under light microscopy, there are certain aspects of our study suggesting future avenues for investigation, particularly with regard to host immune response. Excessive growth may be a consequence of different microenvironments these neoplasms are subjected to, features not readily assessable by light microscopy. Our observation of more frequent PC infiltrates within GBCC suggests an area worthy of further investigation, and further investigation of T-cell subsets within the host immune response may provide additional information regarding the complex relationship between host immune response and capacity for tumor growth and ultimate size.

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**Conflicts of interest**
There are no conflicts of interest.

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**What is new?**
- The histologic features of giant basal cell carcinoma reflect their large size, with increased overall size, tumor depth, and ulceration compared to conventional BCC.
- Tumor microenvironment may provide clues to giant BCC capacity for large size.

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