

## Infiltrative Basal Cell Carcinoma with Nodal Metastasis in a 74-year-old Female: A Case Report

Reynaldo Gabriel Paulino,<sup>1</sup> John Ricardo Chua,<sup>2</sup> Karen Damian,<sup>3</sup> Erwin Gerard Geron,<sup>2</sup> Clarisse Veronica Mirhan<sup>1</sup>

<sup>1</sup>Department of Laboratories, University of the Philippines-Philippine General Hospital, Manila, Philippines

<sup>2</sup>Department of Orthopaedics, University of the Philippines-Philippine General Hospital, Manila, Philippines

<sup>3</sup>Department of Pathology, University of the Philippines, College of Medicine, Manila, Philippines

### ABSTRACT

Basal cell carcinoma, the most common human malignancy, has a rare incidence of metastases ranging from 0.0028-0.55%. We report a case of a 74-year-old female with a 10-year history of an enlarging anterior thigh nodule. Wide resection and inguinal lymph node dissection revealed an infiltrative basal cell carcinoma with lymph node metastasis due to the presence of basaloid cells, limited peripheral palisading, loose stroma, extensive spread, perineural invasion and immunoreactivity to p40, BerEP4, and GATA3.

*Key words:* basal cell carcinoma, X-ray, squamous cell carcinoma in-situ, infiltrative basal cell carcinoma, basaloid cells

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*Corresponding author:* Reynaldo Gabriel T. Paulino, MD

*E-mail:* paulinotomy@gmail.com

*ORCID:* <https://orcid.org/0009-0006-4354-0308>

### INTRODUCTION

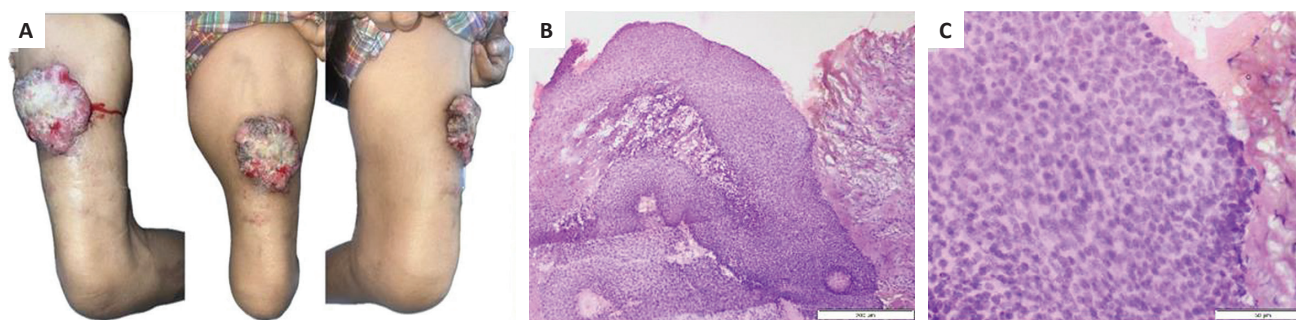
Basal cell carcinoma (BCC) is the most common human malignancy and accounts for approximately 80% of all cancers of the skin. This condition is commonly seen in middle aged men and young women, and people with I-II Fitzpatrick skin phototype with sensitivity to ultraviolet (UV) radiation. Additionally, chronic exposure to arsenic, radiation treatment, and several congenital syndromes are also at risk for developing BCC. The pathogenesis of BCC involves genetic susceptibility compounded with sporadic UV exposure and eventual UV-induced mutations. The histomorphologic findings specific to this BCC subtype (infiltrative) include ulcerating or scar-like pink papules or plaque, variably sized nests of basaloid tumor cells infiltrating normal dermal collagen, and irregular permeating pattern of invasion at the deep tumor edge with possible perineural invasion. Immunoreactivity with BerEP4 is also desirable for the establishment of the diagnosis.<sup>1-3</sup>

### CASE

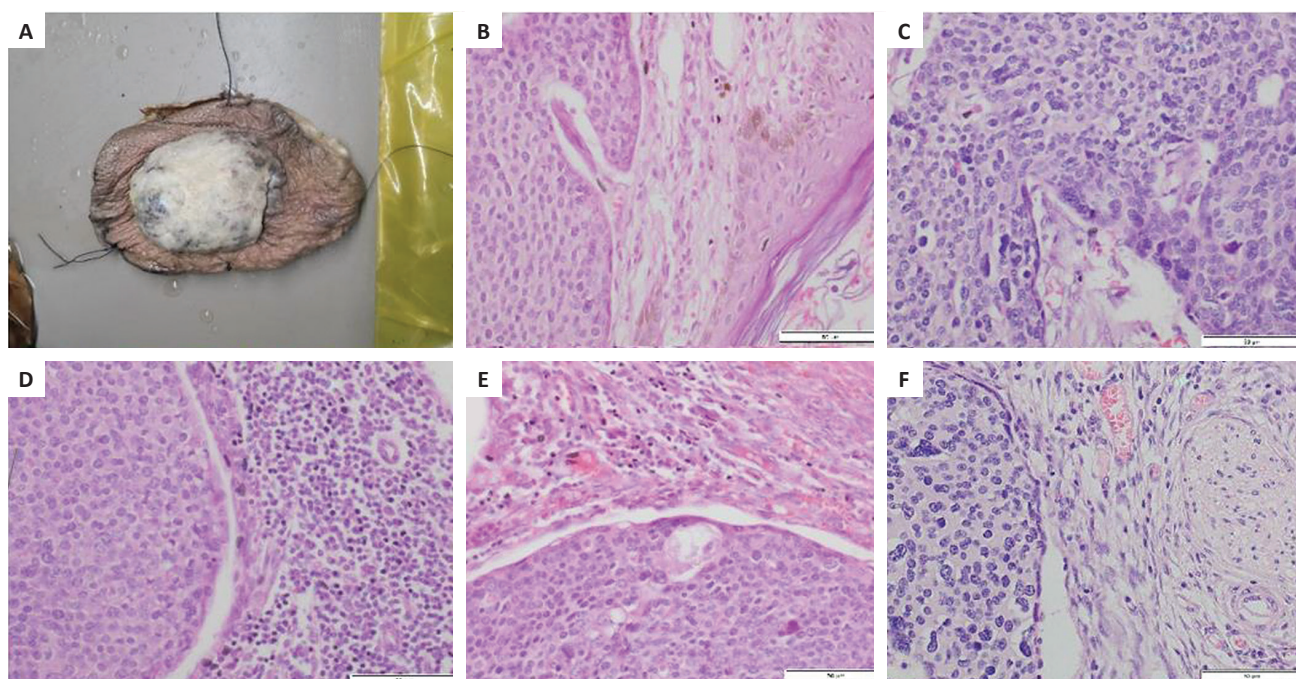
We report a case of a 74-year-old female with a 10-year history of a palpable nodule on the anterior thigh. Consultation was done at a local hospital where surgery was advised. No other work-up, imaging, or intervention was done. In the interim, the nodule progressively enlarged. Three years prior to the present consult, ulceration of the mass was noted secondary to chronic scratching. No consultation was done. The patient treated this lesion by dressing the wound. The mass became fungating with purulent, foul-smelling discharge and occasional bleeding. A left thigh wedge biopsy was done at the Philippine General Hospital revealing a carcinoma in-situ (Figure 1).

Magnetic resonance imaging (MRI) revealed a lobulated mass involving the metaphyseal and diaphyseal portion of the distal femur with para-osseous soft tissue component and mass effects to the distal muscles of the anterior thigh, considerations were osteosarcoma or Ewing's





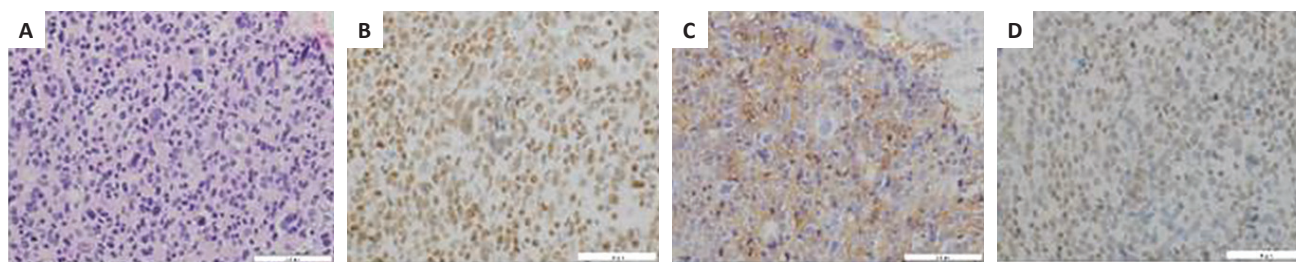
**Figure 1.** (A) 4 x 4 cm fungating, anterior thigh mass with areas of necrosis and punctate bleeding. Nest of tumor cells with large, irregular, hyperchromatic, pleomorphic nuclei, high nucleus to cytoplasm ratio, and mitotic figures described to be at least a carcinoma confined to the epidermis or a carcinoma in-situ (B) H&E, 100x; (C) H&E, 400x.



**Figure 2.** (A) Excised left anterior thigh mass. (B) H&E-stained high-power view or 400x magnification of the mass to skin. (C) H&E-stained high-power view or 400x magnification of the mass. (D) H&E-stained high-power view or 400x magnification of lymph node 1 with tumor cells. (E) H&E-stained high-power view or 400x magnification of lymph node 1 with tumor cells. (F) H&E-stained high-power view or 400x magnification of perineural invasion.

sarcoma. A day after, upon scratching, profuse bleeding of approximately one cup (250 mL) was noted, with associated pallor, dizziness, and loss of consciousness. A chest and abdominal CT scan revealed bilateral pulmonary nodules. On the day of admission, the patient presented with dizziness and five episodes of vomiting of previously ingested food. She underwent blood transfusion and was brought to the University of the Philippines-Philippine General Hospital. On physical examination, a 4 x 4 cm fungating left anterior thigh mass with areas of necrosis and punctate bleeding was noted (Figure 2). Additionally, a 2 x 1 cm lymph node was palpated at the left inguinal region. A wide resection of the anterior left thigh mass, with superficial inguinal lymph node dissection, split thickness skin grafting was performed. All margins were sent for frozen section and were evaluated as clear of tumor. The resection specimens were then processed for evaluation.

Histologically, the cells had large, irregular, hyperchromatic nuclei, prominent nuclear pleomorphism, high nucleus to cytoplasm ratio, and mitotic figures. This was then signed out as a malignant neoplasm, likely carcinoma, 8.3 cm in greatest tumor dimension, positive for skin ulceration and perineural invasion. There was tumor involvement in two out of twelve superficial inguinal lymph. Negative for tumor involvement in all surgical margins of resection. An immunohistochemistry panel of p40, BerEP4, and GATA3 was recommended for an initial panel (Figure 3). The immunohistochemistry results together with morphologic findings of small irregular clumps of basaloid cells, limited peripheral palisading, loose stroma, extensive spread, and perineural invasion can be seen and other essential characteristics present in the cells of interest favour a diagnosis of an infiltrative basal cell carcinoma (Figure 3).



**Figure 3.** (A) H&E-stained high-power view or 400x magnification of malignant cells. (B) Immunohistochemistry study with p40 shows moderate, patchy, nuclear immunoreactivity under high-power view or 400x magnification. (C) BerEP4 shows moderate to strong, diffuse, cytoplasmic membranous immunoreactivity under high-power view or 400x magnification. (D) GATA3 shows moderate, focal, nuclear immunoreactivity under high-power view or 400x magnification.

Table 1. Differential diagnoses											
Differentials	Morphology	CK5/6	BerEp4	P63	P40	BCL2	CD10	EMA	CEA	CK20	
<b>Basal cell carcinoma (and its subtypes)</b>	Basophilic nucleus without a discernible nucleolus and scanty cytoplasm arranged in nests without keratinization. Stromal changes may be present, from a fibromyxoid change to retraction due to deposits. <sup>10</sup>	+	+	+	+	+	+	-	-	-	
<b>Basaloid follicular neoplasm</b>	Trichoepithelioma and trichoblastoma are composed of basaloid cells which may have peripheral palisading, papillary mesenchymal bodies, and a loose to fibrotic stroma. A basaloid follicular hamartoma is composed of basaloid and squamoid cells that only arise where normal hair follicles are present with a loose, cellular or myxoid stroma and possibly with horns, cysts, and pigmentation. <sup>11</sup>	-	-	-	+	+	+	-	-	-	
<b>Basaloid squamous cell carcinoma</b>	Increased N:C ratio, scant amphophilic cytoplasm, and oval and hyperchromatic nuclei without prominent nucleoli. Tumour islands exhibit basaloid cells with areas of comedo necrosis and focal keratinization. <sup>12</sup>	+	-	+	+	-	-	+	+	-	
<b>Sebaceous carcinoma</b>	Sheets of atypical basaloid cells to sebocytes in sheets or lobules separated by fibrovascular stroma. <sup>13</sup>	-	-	-	-	-	-	+	-	-	
<b>Merkel cell carcinoma</b>	Small round blue cell tumour with a high N:C ratio, round/oval nuclei, finely dispersed chromatin, indistinct nucleoli and scant cytoplasm. <sup>14</sup>	-	-	-	-	-	-	-	-	+	

## DISCUSSION

Basal cell carcinoma (BCC) is a carcinoma that arises from the interfollicular or follicular epithelium and is the most common skin malignancy worldwide. The incidence of this condition is inversely related to a country's geographic latitude combined with the pigment status of its inhabitants, with Australia having the highest incidence worldwide.<sup>3</sup> The risk of developing BCC increases with age and shows a predilection for elderly men and young women. The latter is attributed to the use of indoor tanning machines and better health seeking behaviour. Other risk factors include exposure to intense ultraviolet radiation, chronic arsenic exposure, radiation treatment in the young. All patients with Gorlin syndrome develop BCC and people with xeroderma pigmentosum, Bazex-Dupre-Christol syndrome and Rombo syndrome are also at risk of developing BCC.<sup>4,5</sup> The genes that regulate melanin production, *MC1R*, *ASIP* and *TYR*, if with polymorphisms, increase the risk of BCC.<sup>6</sup> This disease is brought about by an interplay of genetic variables and ultraviolet induced mutations. 58-69 % of sporadic cases of BCC are due to the loss of heterozygosity in the *PTCH1* gene. *TP53* gene alterations (loss of heterozygosity) can also be seen in 40-65% of sporadic cases and is due to *PTCH1*, leading to a dysregulation in cell cycle arrest, apoptosis, and DNA repair.<sup>7</sup>

Clinically, mostly in the head or neck, this may present as pink papules and plaques that would frequently ulcerate which would then present as a scar-like lesion. Metastasis is an extremely rare finding observed in approximately 0.003% to 0.5% of all cases reported.<sup>8</sup> A study done in America noted eleven cases of metastatic BCC from 2005 to 2018, 8 of which were infiltrative basal cell carcinoma.<sup>9</sup> Another study done in Brazil used data from 1894 to 2017 with a total of 389 cases of metastatic BCC with 178 or 45% of these manifesting with lymph node metastasis.<sup>10</sup> There are no noted cases of metastatic basal cell carcinoma in the Philippines as of now. Several risk factors have been proposed to be associated to metastasizing BCC such as large tumor size, deep invasion, repeated local recurrence, the infiltrative subtype with presence of perineural or perivascular invasion, history of radiation, location in the central portion of the face or ears, long period of evolution, squamatisation, and possibly immunosuppression.<sup>9,10</sup> The pathways of tumor metastasis are lymphatic or hematogenic wherein the most common site of metastasis is the lymph nodes followed by the lungs.<sup>10</sup> Histologically, all types of BCC display basaloid tumor cells with a hyperchromatic nuclei and scant cytoplasm. These tumor cells may vary in size and shape, and apoptotic cells may also be seen within the nests. Stromal changes range from a fibromyxoid change to the retraction of nests from stroma, calcification, and amyloid deposition. For the Infiltrative subtype as shown in this case, variably sized, jagged nests of basaloid

tumor cells would be seen infiltrating the normal dermal collagen in an irregular permeating pattern at the deep tumor edge with or without perineural invasion.<sup>2,8</sup>

Immunohistochemical staining is a useful tool in differentiating BCC from the differential diagnoses. BCC expresses p40, p63, and CK5/6, strongly. For BCL2 and CD10, BCC would have a diffuse positivity as well as a focal expression of AR. Negative stains that would rule BCC out from the other differentials are EMA, CEA, and CK20. For the next differential, basaloid follicular neoplasm, this would stain positive in CK20, stromal CD10, and peripheral BCL2. Basaloid squamous cell carcinoma would stain positive in EMA, p40, p63, CEA and negative for BerEP4. Sebaceous carcinoma would stain positive in EMA and negative in BerEP4. Merkel cell carcinoma would be diffusely positive in CK20 with a perinuclear dot-like positivity and would also stain diffusely in neuroendocrine markers.

Surgery and radiotherapy are the most common modalities. But since 2012, a more specific therapeutic modality emerged for patients that are not candidates for surgery or radiotherapy in the form of the inhibitors of the Hedgehog signalling pathways (Vismodegib and Sonidegib). They, however, are associated with a low tolerability and high rate of adverse events such as muscle spasms, dysgeusia, weight loss, alopecia, and fatigue. The rate of response to these therapeutic modalities for metastatic disease vary between 15% to 37%. Another immunotherapy agent was approved back in 2021 for patients with locally aggressive BCC that has not responded to Hedgehog inhibitors or in patients with metastatic BCC in whom Hedgehog inhibitors are not appropriate, Cemiplimab. This drug targets the PD-1 (programmed cell death-1) receptor on T and B cells and demonstrated clinically meaningful antitumor activity, including durable responses, and an acceptable safety profile in patients with metastatic BCC who had disease progression on or intolerance to Hedgehog pathway inhibitor therapy.<sup>10,15</sup>

## CONCLUSION

Basal cell carcinoma and its subtypes is a common disease entity usually associated with a PTCH1 mutation. The diagnosis is made by clinical information complemented with a histopathologic evaluation. Surgical excision is the treatment modality of choice. Though nodal metastasis of the basal cell carcinoma cells is an extremely rare occurrence, lymph node involvement should still be investigated if clinically and radiologically warranted.

## ETHICAL CONSIDERATIONS

Patient consent was obtained before the submission of the manuscript.

## STATEMENT OF AUTHORSHIP

All authors certified fulfilment of ICMJE authorship criteria.

## AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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None.

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