Case Presentation Protocol
2018 Hot Spots in Dermatology

A Case Study of Metastatic BCC

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Financial Disclosures and Affiliations

Dr. Roman W. Glamb, MD and Marianna F. Karewicz, NP have no financial relationships to disclose. Both are affiliated with Straub Medical Center.
Abstract

Basal Cell Carcinoma (BCC) is deemed as one of the most frequent types of skin cancer. Typically, it is regarded as localized in nature and there is a tendency to view the condition as non-malignant because the tumor rarely metastasizes (Habif, 2016). However, what if the condition became aggressive? If left untreated, BCC has the capability to spread through direct extension, destroying normal tissue and large portions of the body; even penetrating the subcutaneous tissue to bone and/or the brain.

This case presentation will explore the aggressive nature of BCC and depiction of its metastatic nature if left neglected.
Basal Cell Carcinoma

Eighty five percent of the time Basal Cell Carcinoma (BCC) appears on the head and neck. Twenty five to thirty percent occur on the nose, which is the most common site. BCC is rarely found on the back of the hands. It may be found on sites where there is no ultra violet exposure, for example the genitals and breasts. The epidemiology of BCC constitutes that the average lifetime risk for Caucasians to develop BCC is thirty percent. It is most common in adults, especially the elderly. Other risk factors include: 1. Fair skin, 2. Blonde/Red Hair, 3. Light eye color, 4. Poor tanning ability (Fitzpatrick skin type I), and 5. Sun damage skin. The male to female ratio is 2:1. Women younger than forty years old outnumber men. Living closer to the equator increases the risk. The pathogenesis includes as a main risk factor ultra light exposure (UVA & UVB) which damages DNA. Transplant patients are 10 to 100 times higher at risk than general population. There is a 10 fold increase of another BCC, 3 years status post initial BCC diagnosis. BCC occurs at sites of trauma, scars, thermal burns and injury. Also, develops years later at sites treated with ionizing radiation. The tumor appears 3 months to over 7 years at the site of the previous injury.

Pathophysiology

BCC derives from basal keratinocytes located in the epidermis and adnexal structures such as hair follicles and eccrine sweat ducts. UVB damages DNA and the repair system altering the immune system. The tumor grows by direct extension, requiring the surrounding stroma for support. The nature of the cancer is unpredictable. It may remain small for years or grow rapidly with extension of the tumor with some regression. The types of BCC include: 1. Nodular (21%), 2. Superficial (17%), 3. Micronodular (15%), 4. Infiltrative (7%), 5. Morpheaform (1%), 6. Mixed pattern.
History

The patient ("J.M") is a 75 year old Caucasian male from Kauai’i. He presents with a BCC of the skin with metastatic disease involving the liver, lungs, lymph nodes. He is status post radiation therapy to a neglected bleeding left shoulder tumor and a low back lesion. He has been diagnosed with Neuroendocrine Cancer involving the left axilla/region mass. He has undergone palliative radiation and underwent chemotherapy with his oncologist on Kauai’i with Vismodegib for known metastatic disease within the axilla and lung but it had to be discontinued because of side effects. Also, he underwent treatment with radiofrequency ablation for a single known liver metastasis.

He presents as a new patient to the Dermatology Department for a skin check and skin cancer screening (10/10/2017).

Social and Family History

Patient reports having two years of college. He is a Vietnam War Veteran and has worked several years in construction and hotel management. He owns a concrete company and has been a farmer for over twenty years. In the past, he also worked on Johnston Atoll/Island (Air force base which has also been used for military missile testing and chemical weapon, Agent Orange storage and disposal site) for approximately two years. He admits to not wearing any sun protection and having exposure to radiation.

There is no family history of skin cancer. His mother had a history of Cardiovascular Disease and lived until age 93 years old. His grandfather had a history of smoking cigarettes and died of Lung Cancer. J.M. has a brother who is in good health. He reports that he has no significant medical problems.
Past Medical History

The patient’s condition timeline included the following: 1. History of multiple BCC of various sites 2. Left shoulder and back tumors irradiated with good results 3. Liver mass biopsy result malignant 4. He started on Vismodegib with good response with exception to left axillary region which developed rapid enlarging mass. Biopsy was performed and showed neuroendocrine tumor. The latter increased his pain and he underwent palliative radiation to the axillary mass. 5. During the ten fraction course, decrease in pain occurred with mass regression. He completed the treatment on 06/16/2017. 6. The tumor regressed further to the point of no detection by the patient. 7. He began systemic therapy with Carboplatin and Etoposide. 8. Currently, he is receiving chemotherapy Neulasta for the metastatic neuroendocrine carcinoma.

Left supraclavicular region ulcerated wound at the site of ulcerated BCC with skin change and consistent with neoadjuvant radiation therapy; 4-2.5 cm in size, March 2016.

March 2016
June 02, 2016

June 30, 2016

Left shoulder s/p radiation therapy for locally advanced BCC

PATHOLOGY DIAGNOSIS
Left shoulder: BASAL CELL CARCINOMA, nodular and sclerosing
Margins involved

Comments: Dr. David Lin reviewed the case and agreed with the
diagnosis.

TYP/sg/6/23/2016

CLINICAL DATA: Left shoulder skin cancer <6", 15 year history

PROCEDURE: Punch biopsy left shoulder

GROSS DESCRIPTION
Received one container in formalin labeled "John Smith, left
shoulder." The specimen consists of two pieces of the skin from punch
biopsy of 0.1 cm in maximum dimension. One piece is inked blue, the other is inked red. The specimen is totally
submitted into one cassette.

TYP/sg/6/23/2016

MICROSCOPIC DESCRIPTION
The biopsy reveals an infiltrating neoplasm. The neoplastic cells
show basooid appearance. There is no epidermal involvement. The
neoplastic cells show following immunoreactions:
- Cytokeratin
- Bcl-2
- CD-117
- Melan-A (red)
- HMB
- Chromogranin A

MIC: Negative
CgA: Negative

Negative and positive (internal IT readable); controls show
appropriate results.

***ELECTRONICALLY SIGNED OUT BY YU MO MD, M.D.***

9420 Kuhio Highway, Lihue, HI 96766
Medication

The patient has been taking the following medication: 1. Oncology mouthwash CMD, 10 cc three times per day or as needed for mouth sores. Viscous lidocaine 2%, Benadryl, Nystatin, Predisolone (1:1:1:1). 2. Ondansetron 8 mg tablets, 1 tablet by mouth every 8 hours.
3. Compazine 10 mg tablets, 1 tablet by mouth every 6 hours. 4. Amoxicillin 500 mg capsules, 1 capsule by mouth three times per day. 5. Flexeril 10 mg tablets, 1 tablet by mouth twice per day.

In addition, he has no known drug allergies reported.

Pathology Results and Pathologist’s Findings

All three tumors (left shoulder, liver, and left chest wall) were high grade tumors of similar H&E morphologies. However, they look very different from the usual BCC’s that the patient had. The tumors from the left shoulder and liver were the same tumor staining to a BCC, while the left chest wall tumor was a neuroendocrine carcinoma. The latter was not a Merkel cell carcinoma because CK20 and Merkel cell polyoma virus were both negative.

In consultation with University of California San Francisco (UCSF), there was a mention of a paper (Patel et al) describing recurrent BCC with Neuroendocrine differentiation that may have morphed. We may be seeing a unique case of cell morphology.

Liver biopsy
Liver, core biopsy:
1. POORLY-DIFFERENTIATED CARCINOMA (see Addendum)
   Comment:
   2. Fluorescence in situ hybridization:
      a. Negative for NPM1 rearrangement
      b. Negative for 6q21 (CYY) rearrangement

Addendum Comment
This Addendum is created to incorporate the results of an additional immunohistochemical staining and fluorescence in situ hybridization (FISH) testing (requested after discussion with Dr. L. Wong on May 10, 2016). The requested material was pulled from archive on 5/11/2016.

Given the collective information, the findings still raise the possibility of metastatic basal cell carcinoma (especially given the patient’s prior history of basal cell carcinoma – X15-2146).

The additional FISH testing provides no evidence for Ewing sarcoma/primitive neuroectodermal tumor, clear cell sarcoma, desmoplastic small round cell tumor, extraskeletal myxoid chondrosarcoma, myxoid liposarcoma, rhabdomyosarcoma, angiomatoid fibrous histiocytoma, or synovial sarcoma.

The morphologic and immunohistochemical data do not support hepatocellular carcinoma, mesenchymoma, melanoma, or a hematopoietic malignancy. A neuroendocrine tumor is less favored, given the negative (i.e., synaptophysis) or partial and equivocal/weak (chromogranin A, CD56) labeling by neuroendocrine markers.

Addendum: Histologic Description:
The hepatocellular and eosin-stained sections demonstrate thin core-shaped fragments of liver tissue and an abnormal, malignant population of small to intermediate sized tumor cells. These tumor cells have hyperchromatic nuclei with rounded to irregular nuclear contours and scant cytoplasm. These tumor cells are densely aggregated and do not appear to form any glandular structures. The tumor cells are seen adjacent to liver parenchyma and are also found as detached, fragmented aggregates. Necrotic or granuloma formation is not seen in this sampling.

Immunohistochemical staining was conducted on block 1. The malignant cells stain with cytokeratin 5/6 (diffuse), cytokeratin 7 (diffuse), high molecular weight keratin 34BE12 (diffuse), BER-E24 (diffuse), p63, p63 (partial nuclear, partial weak cytoplasmic), Mep Par-1 (diffuse, weak), CD99 (diffuse, weak), glypican-3 (partial), and BCL-2 (diffuse, variable intensity). The malignant cells have equivocal labeling with vimentin (partial/equivocal), CEA (partial, equivocal), and chromogranin A (partial, weak/equivocal). The malignant cells do not stain with cytokeratin 5/6, SMA, TTF-1, M1, desmin, synaptophysis, CD56 (LCA), S100, and melan A (positive controls appropriate).

Addendum: Special Stains
Immunohistochemical staining - block 1: Cytokeratin 5/6, Cytokeratin 7, Cytokeratin 20, BER-E24, high molecular weight keratin 34BE12, p63, p63, Mep Par-1, CD99 (LCA), CD99, CD99 (MIC2), Chromogranin A, Synaptophysis, Glypican-3, BCL-2, Vimentin, SMA, TTF-1, M1, Desmin, S100, Melan A
Metastatic 10

Chest Wall Biopsy

PATHOLOGY DIAGNOSIS:
LEFT CHEST WALL OPAQUE: NEUROENDOCRINE CARCINOMA (SEE COMMENT)
-Focal necrosis present
-Mitosis estimated about 6/10 hpf

Comments: Differentiated diagnosis includes Merkel cell carcinoma and metastatic neuroendocrine carcinoma. Since the neoplastic cells are negative to CK20, a primary skin neuroendocrine carcinoma, such as Merkel cell carcinoma, is unlikely. Metastatic neuroendocrine tumor from lung is also less likely due to negative TTF-1 immunostain. The finding is most likely a metastatic neuroendocrine carcinoma with unknown primary. Recommend clinical correlation.

The patient has history of basal cell carcinoma in various sites of SKIN (2014-375, 2115-2176, 2016-3360, 3316-1619 and 3316-6932), and poorly differentiated carcinoma in the liver (3316-549). The current tumor in this biopsy appears morphologically similar to but immunohistochemically different from the neoplastic cells found in the liver (3316-649).

Dermatopathologist: Dr. David Liu reviewed the slides and agreed with the diagnosis. Dr. Lekareva notified on 06/09/17.

VNS/1g/5/1/2017

Consultant Addendum
Date Ordered: 6/25/2017
Signed Out: 6/26/2017
Date Complete: By: Jane Garma
Date Reported: 6/28/2017

Consultant Diagnosis
LEFT CHEST WALL OPAQUE: HIGH-GRAND NEUROENDOCRINE CARCINOMA

Consultant Comment
The above diagnosis was rendered by Dr. Grace E. Kim, UCSF,
Department of Pathology, 1813 4th Street, M1260, San Francisco, CA
94158. See attached report for details of consultation (Accession
No.: 517-16716: 06/21/17).

Consultant Addendum
Date Ordered: 10/10/2017
Status: Signed Out
Date Complete: 10/10/2017
By: Jane Garma
Date Reported: 10/10/2017

Consultant Diagnosis
LEFT CHEST WALL OPAQUE: INVOLVED BY NEUROENDOCRINE CARCINOMA,
HIGH-GRAND
Review of Systems

Patient has reported that he has never smoked. He denies using smokeless tobacco. He drinks about 0.6 oz of alcohol per week. He denies any illicit drug use. In addition, there was a negative report from the patient for the remainder of the points of the review of systems.

Physical Examination

Complete skin examination of the face, neck, chest, abdomen, back, arms and legs was performed. The patient has severe actinic damage. Examination of the oral mucous membranes reveals no significant actinic damage. The patient had no adenopathy. He has a clinically obvious squamous cell on his right forearm. A possible Squamous Cell Carcinoma (SCC) 7 mm on the right forearm was treated with biopsy followed by curettage and electrocautery. Alternative treatment discussed and understood. Patient was warned of the possibility of scarring, recurrence and the need for follow-up. Multiple actinic keratoses on both upper extremities were present. He had the sequelae of radiation therapy on his left chest in the sequelae of the extensive excisions on the back.
Treatment and Recommendations

Over 15 actinic keratoses on the upper extremities were treated with Aldara. Proper application of Aldara, in this case once a day for 2 weeks, rest for 2 weeks, and then a second cycle of once a day for 2 weeks was implemented. Discussion of expectation of treatment, in regards to an appropriate inflammatory response was reviewed. The patient was instructed in the proper use of sunscreen and sun protection. We also discussed the risks and benefits of vitamin D supplementation. Nicotinamide (Vitamin B3) 500 mg, two times per day was also recommended.

Conclusion

Basal Cell Carcinoma is a multifaceted and unpredictable condition. Although, it is typically localized, the tumor has the ability to spread extensively and effect large portions of the body as well as multiple organ systems. This should be kept in mind for the clinician in regards to the approach and education of the condition to the general population.

The final posed question pertaining to this case study is the following, “Is it really only BCC metastasizing?”
References


Patel et al. BCC with progression to metastatic neuroendocrine carcinoma. Rare Tumors 2010; 2 e8.