Unusual Carcinomas

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Introduction

- The goal of the presentation is to acquaint you with some uncommon skin cancers and novel settings in which skin cancers may be expected.
- Verrucous carcinoma
- Adenocarcinoma arising in EM Paget’s disease
- Vemurafenib induced carcinomas
Audience Response

Click for entities that you have seen:

1. Verrucous carcinoma
2. Adenocarcinoma arising in invasive EM Paget’s disease
3. Vemurafenib associated carcinoma
Skin Cancer Prevalence

- Approximately 1,000,000 non-melanoma skin cancers are diagnosed each year in the United States
- Of these roughly 80% are basal cell carcinomas
- 20% are squamous cell carcinomas
- Small percentage of rare carcinomas
- High likelihood of encountering skin cancers in daily practice
Verrucous carcinoma

- Rare variant of squamous cell carcinoma
- First described in the oral cavity by Dr. L. Ackerman in 1948
- Clinically characterized as a slowly growing verrucous plaque at a variety of body sites (oral, genital, extremities)
- May be locally destructive but seldom metastasizes
Verrucous carcinoma

- Treatment is mainly surgical
- Large size of tumor and anatomic considerations lead to propensity for local recurrence
- May occasionally give rise to a high grade invasive squamous cell carcinoma, especially in large lesions of long standing
- Role of radiation is controversial
Photos courtesy of Dr. L. Requena
Verrucous carcinoma histopath

- Usually a large sessile lesion
- Characterized by an exo-endophytic growth pattern
- “Pushing” rather than infiltrative margins
- “Deceptively” bland cytology
- Glassy eosinophilic keratinocytes
- Low mitotic activity
- Ample parakeratosis
Immunohistochemistry

- Keratin is positive
- p53 usually noted just along basal layer, unlike more conventional SCC which shows more haphazard changes
- Ki-67 low and also at basal layer
- p16 typically negative
P53
Human Papilloma virus

- Is seldom found in association with verrucous carcinoma
- When papilloma virus is present transcriptionally activated mRNA is not indicating that there is likely no causal role of papilloma virus in the generation of this type of carcinoma
- Some have advocated use of papilloma virus testing to aid in the differential diagnosis of this lesion
Pitfalls

- Small biopsies may not demonstrate all of the features and lead to a benign diagnosis
- Bland cytomorphology may lead to misdiagnosis as a benign lesion
Summary

- Large slowly growing tumor at a variety of body sites
- Characteristic architecture
- Bland cytomorphology
- Clinico-pathologic correlation important
- Small biopsies may be misleading
Adenocarcinoma in EMPaget’s disease

- Extramammary Paget’s disease is a rare tumor of uncertain origin
- Has been a “wastebasket term” and “primary” and “secondary” forms exist
- Primary thought to arise from either apocrine glandular or a stem cell in the epidermis
- Secondary indicates cutaneous involvement by an underlying visceral carcinoma (colon, bladder, prostate)
- Arises typically in apocrine rich areas including groin, perianal and scrotal areas
- Invasion is rare and portends a poor prognosis
Adenocarcinoma in EMPD

- Typically a disease of older individuals (60’s-)
- Treatment is primarily surgical (with high recurrence rates)
- Rare occurrence in EMPD(<10%) but exact figures hard to ascertain
- Some advocate measurement of invasive component as tumors > 1 mm in depth have worse prognosis with a greater propensity for lymph node and distant metastasis
Adenocarcinoma in EMPaget’s disease

- Invasive cases may spread to regional lymph nodes and metastasize to distant sites
- Her-2-neu amplification has been shown to portend a greater propensity for invasion, persistence, and nodal metastasis
- This may be also be a therapeutic target
Photos courtesy of Dr. L. Requena
Adenocarcinoma histopathology

- Typical intraepidermal changes of EMPD present
- As Paget’s may involve a very broad areas and result in large excisions careful scrutiny is necessary
- Immunohistochemistry is helpful in the differential diagnosis and potentially helpful in identifying small invasive foci, but beware in that normal glandular elements can be confounding
- One study demonstrated higher Ki-67 labelling rates and expression of cyclin D-1 in invasive versus non-invasive EMPD
- Serum Carcinoembryonic antigen (CEA) levels have also been shown to be elevated in invasive disease
Cytokeratin 7
Summary

- Rare complication of Extramammary Paget’s
- Sampling important
- Thickness of lesion portends prognosis
Vemurafenib

- Novel anti BRAF treatment
- Used in the treatment of metastatic melanoma that harbors a BRAF V600E mutation
- Shown to increase survival time in patients with metastatic melanoma that harbors this mutation
- A variety of cutaneous side effects have been described both benign and malignant
Vemurafenib

- 39-year-old woman with a 7 year history of an irritated lesion on the plantar left foot previously diagnosed as a plantar wart
- Four month history of an enlarging subcutaneous mass on the left calf
Ulcerated T4b primary melanoma

10X Melan-A

20X Ki-67

Courtesy of A. Naujokas
Staging workup

- Primary Lesion: 10 mm thick ulcerated acral melanoma primary.
- Left calf: nodal melanoma metastases.
- Multiple other chest wall lesions noted, fine needle aspiration of a right chest lesion consistent with metastatic melanoma.
- Testing revealed a BRAF V600E mutation.
Stage IV BRAF mutant melanoma

- Vemurafenib is a BRAF inhibitor that confers objective tumor responses in half of patients treated.

- Patient opted to initiate Vemurafenib
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D.,
John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D.,
Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D.,
Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D.,
Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D.,
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Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A.,
Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D.,
and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group®

Overall survival (HR 0.37)

Progression-free survival (HR 2.6)
960mg BID: Developed joint pain, muscle aches, rash

Resolution of side effects with reduction in dose to 480mg BID
10 weeks on Vemurafenib

5mm crateriform papule on the right cheek

Courtesy of A. Naujokas
Most Common Adverse Events

- occurring in >5% of patients

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Chapman et al., NEJM 2011
Vemurafenib lesions

- Verrucous keratoses (HPV does not seem to be causal)
- Grover’s disease/Warty dyskeratoma
- Keratosis pilaris
- Actinic keratosis
- Keratoacanthoma/Squamous cell carcinoma
- Rarely aggressive phenotypes
Vemurafenib

- Mechanism of action unclear
- Binding of inhibitor to wild type BRAF (in keratinocytes) though to activate the MEK/ERK kinase pathway and promote growth
- Thought to promote growth in keratinocytes that have previously acquired a RAS mutation
- Carcinomas typically present relatively soon after therapy is initiated (days to weeks)
Treatment

- Typically traditional treatments employed
- Electrodesiccation
- Curettage
- Surgical
- Retinoids have been tried in patient’s with multiple or eruptive lesions
Summary

- Used in patients with metastatic melanoma with a V600E mutation
- Keratinocytic neoplasms thought to be the result of paradoxical activation of wild type BRAF
- Present soon after initiation of therapy
- No specific histopathologic correlate
- Respond to standard treatment