U019
Game Changers in Dermatopathology

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• DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

  • I do not have any relevant relationships with industry

  • Off Label Usage
    • No
Learning Objectives

• Review and update what’s new in Dermatopathology
• Summarize a game changer and how it impacts the practice of dermatopathology
Dysplastic Nevi with Positive Margins
To re-excise or not to re-excise?

How do you manage dysplastic nevi in your practice?

A. Re-excise all dysplastic nevi (mild, moderate, or severe) with positive margins
B. Re-excise only moderately and severely dysplastic nevi with positive margins
C. Re-excise only severely dysplastic nevi with positive margins
D. Don’t re-excise dysplastic nevi
Dysplastic Nevi with Positive Margins
To re-excise or not to re-excise?

Consensus Statement
Addressing the Knowledge Gap in Clinical Recommendations for Management and Complete Excision of Clinically Atypical Nevi/Dysplastic Nevi Pigmented Lesion Subcommittee Consensus Statement

Caroline C. Kim, MD; Susan M. Swetter, MD; Clara Curiel-Lewandrowski, MD; James M. Grichnik, MD, PhD; Douglas Grossman, MD, PhD; Allan C. Haberm, MD; John M. Kirkwood, MD; Sancy A. Leachman, MD, PhD; Ashraf A. Marhambo, MD; Michael E. Ming, MD, MSCE; Kolly C. Nelson, MD; Emil Yavuzer, PhD; Sarg S. Venna, MD; Suich Y. Chen, MD, MS

Objective:
• To determine outcomes and risk for the development of subsequent cutaneous melanoma from moderately dysplastic nevi that had an excisional biopsy with positive histologic margins observed for ≥ 3 years

Design:
• Multicenter (9 US academic dermatology sites) retrospective cohort study
• Patients ≥ 18 years of age with a moderately DN that had an excisional biopsy with + histology margins with ≥ 3 years of clinical f/u
• Central dermatopathology review: 5 representative slide cases were reviewed per site to confirm histologic grading

Main outcomes and measures:
• Development of melanoma at 1) the same biopsy site or 2) elsewhere on the body
Results:

467 moderately DN + margins from 438 patients with a mean f/u time of 6.9 years.

- **No biopsy-site melanomas developed**
- 100 patients (22.8%) developed a *cutaneous melanoma at a separate site*

Multivariable analysis revealed that history of cutaneous melanoma was significantly associated with the risk of subsequent melanoma at a separate site (OR 11.74; 95% CI: 5.71-24.15; p<0.001) as were 2 or more prior biopsied dysplastic nevi (OR 2.55; 95% CI, 1.23-5.28, p=0.1).

Central dermatopathology review:

- Agreement in 35 of 40 cases (87.5%)
- 3 of 40 cases upgraded in degree of atypia. Of these, 1 was interpreted as melanoma in situ. That patient remains without recurrence or evidence of melanoma after 5 years of follow-up.
Dysplastic Nevi with Positive Margins
To re-excise or not to re-excise?

**Conclusions**

- Excisional biopsy for highly suspicious lesions
- 1-3 mm clear clinical margins recommended for excisions
- Be aware of limitations of partial/incisional biopsies
- Close observation with routine surveillance of moderate dysplastic nevi that had an excisional biopsy with + histologic margins may be reasonable
- If observing, clinician and patient should monitor biopsy sites for unusual regrowth
- However, having 2 or more prior biopsied dysplastic nevi (1 of which is moderately dysplastic) appears to be associated with an increased risk for melanoma at a separate site—recommend continued surveillance.
- Future larger scale data: other subtypes of nevi, outcomes, margin types, patient populations
What’s New in Dermpath?

- Another IHC stain
Muir Torre syndrome and immunohistochemical testing
Muir Torre syndrome and immunohistochemical testing

- Pathology diagnosis of sebaceous adenoma, sebaceous carcinoma, or reticulated acanthoma with sebaceous differentiation
- *This sebaceous neoplasm may be associated with Muir Torre syndrome, a variant of hereditary nonpolyposis colorectal cancer (HNPCC). If clinically indicated and patient consent is obtained, immunohistochemical stains and/or microsatellite instability testing may be performed to further evaluate for defective DNA mismatch repair (a marker for HNPCC).*
- 91% of ASDP survey respondents ordered this test only when the clinician requested it
Muir Torre syndrome and immunohistochemical testing

- MSH2 & MSH6; MSH6; PMS2; MLH1&PMS2
- IHC loss of lesional nuclear immunoreactivity
An antigen isolated in patients with metastatic melanoma

- 4+ diffuse nuclear positivity (sensitivity of 67% and specificity of 100%) is associated with malignant melanoma
- May aid in the diagnosis of borderline lesions, i.e., severely dysplastic nevus versus melanoma; may help identify nevoid melanoma
- Maybe useful for nodal nevus versus metastasis if primary tumor is positive
- May help in margin evaluation in MIS on chronic, sun-damaged skin

Pitfalls occur
- Lowest positivity (35%) with desmoplastic melanoma
- 14% of nevi positive; 15% of solar lentigines positive
- MCC can also be positive
- Unequivocal melanoma sometimes negative

Not yet a substitute for H & E, Melan A, SOX10
PRAME
Merkel Cell Polyoma Virus (MCPyV)

- 80% of MCC have MCPyV
  - Associated with a better prognosis
BAP1 Inactivated Melanocytic Tumor
BAPoma/Weisner’s nevus

- Skin-colored dome-shaped papule
- Dermal, often combined nevus
- Epithelioid cells
- Frequent TILs
- IHC loss of nuclear BAP1 expression
- BRAFV600E mutation

What’s New in Dermpath?

• H & E is KING 🏷

• The best special stain in Dermpath is DEEPER LEVELS in the block, not a special stain

• BIG fixation on IMMUNOSTAINS which just run up a big bill and may color what you don’t know a different color

• But, sometimes you need them

• IHC stains improve our diagnostic capabilities and help guide therapy

• Health care cost needs to be considered

J Cutan Pathol 2020; 47:896-902
The Molecular Era in Dermatopathology
Deep Penetrating Nevus

- Darkly pigmented
- Most common in the 1st 3 decades
- Occurs on the head & neck (35% of cases), trunk (25%) and upper extremities (20%)
- Dermal wedge-shaped heavily pigmented melanocytes & melanophages
- Intermediate/indeterminant risk because infrequently progresses to melanoma
Deep Penetrating Nevus

- Molecular testing assists with diagnosis and prognosis
- Characterized by mutations in $\beta$-catenin & MAPK (mitogen activated protein kinase)
  - Mutations of the $\beta$-catenin pathway change the phenotype of a common nevus with BRAF mutation into that of DPN, with increased pigmentation, cell volume and nuclear cyclin D1 levels

(Overheard) Quandaries about Spitz Neoplasms

• >70 years ago, Sophie Spitz, a brilliant pathologist, raised similar questions that are still pertinent today in the molecular era

  • Is a Spitz nevus benign?
  • Do I need to re-excise? How wide?
  • What if the report says “atypical”?
  • What is an “atypical Spitz tumor”?
  • But the patient is a kid! It’s not melanoma.
  • But the patient is an adult! It’s not a Spitz nevus.
  • Spitz nevi turn into melanoma.
  • SLNB will tell us what it really is.
  • Molecular studies will tell us what it really is.
Atypical Spitz Neoplasms in the Molecular Era

• FISH (fluorescence in situ hybridization) better for smaller lesions
• Conventional or microarray CGH (comparative genomic hybridization)
• NGS (next generation sequencing)
# Current Paradigm for Atypical Spitz Neoplasms in the Molecular Era

<table>
<thead>
<tr>
<th></th>
<th>Melanoma</th>
<th>Spitz Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal aberrations</td>
<td>95%</td>
<td>Chimeric fusion proteins: Ros, ALK, NTRK, BRAF, RET, MET</td>
</tr>
<tr>
<td></td>
<td></td>
<td>***Nevi can have a BRAF mutation</td>
</tr>
<tr>
<td>Common gains</td>
<td>6p, 7q, 17q, 20q, 4q, 8q, 1q, 11q</td>
<td>Isolated gain in 11p, some with 7q gains</td>
</tr>
<tr>
<td>Common deletions</td>
<td>9p,10, 6q, 21q, 8p</td>
<td>3p21, 6q23, heterozygous loss of 9p21</td>
</tr>
<tr>
<td>***Homozygous 9p21 deletion (loss of CDNK2A) a/w ↑ risk of metastasis and death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tert promoter mutations</td>
<td>Common ~60%</td>
<td>Uncommon, but can be seen in some dysplastic and other atypical nevi</td>
</tr>
<tr>
<td>***Marker for aggressive behavior/clinical course</td>
<td></td>
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</tr>
</tbody>
</table>
Atypical Spitz Neoplasms in the Molecular Era

Kinase fusions are frequent in Spitz tumors and Spitzoid melanomas, and most are indolent in Spitz tumors.

- The detection of kinase fusions in ~50% of Spitz melanocytic neoplasms has provided a framework for better understanding of Spitz tumor development.
- As these fusions may be detected across the entire spectrum from benign to malignant, kinase fusions are thought to represent an early oncogenic event.

Clinicopathological/genomic correlation studies with different fusions, e.g. ALK fusion a/w exophytic/polyoid lesions and fusiform/plexiform nests in AST.

- As specific kinase fusions become more readily identified and better characterized, it will be possible to determine if specific histologic features align with the presence of particular kinase.
- The presence or absence of a kinase fusion may provide additional insight into the predicted outcome of a particular lesion.
Summary

*Indeterminant Melanocytic Neoplasms in the Molecular Era*

- Molecular testing is appropriate when a diagnosis of melanoma is in question
- Indeterminate melanocytic neoplasms (Atypical Spitz neoplasms, MELTUMP, DPN)
- Assists in diagnosis, prognosis and potentially treatment
- Health care cost needs to be considered

Kim et al. BRAF fusion Spitz neoplasms: clinical, morphologic, and genomic findings in 6 cases. *J Cutan Pathol*. 2020;47:1132-1142
When confronted with a patient who has melanoma

• Is this melanoma high risk?
  • Prognostic uncertainty in melanoma
  • SLNB
  • GEP testing: identify “high risk” on a molecular level
• The value of a prognostic test is to improve staging accuracy and management plan for patients who could receive more frequent follow-up, imaging, adjuvant therapy, and potential enrollment in clinical trials
From Mayo’s scientific finding to clinical application: bench to bedside

Unmet need

• A test to identify patients with a low risk of SLN metastasis that could safely forgo a SLNB

• Such a test could prevent unnecessary SLNB, avoid complications, and reduce health care costs

The lab of Dr. Alexander Meves

Discovery

• The goal was to develop a Gene Expression Profile molecular based test in combination with Clinico-Pathological variables (age and Breslow depth)

• PCR on FFPE tissue-biopsy or excisional biopsy specimen from T1-3 cutaneous melanoma patients

CP-GEP Model

<table>
<thead>
<tr>
<th>Gene (protein)</th>
<th>Gene Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLANA (melanoma antigen recognized by T-cells 1)</td>
<td>Melanosome biogenesis</td>
</tr>
<tr>
<td>GDF15 (growth differentiation factor 15)</td>
<td>Epithelial-mesenchymal-transition (EMT)</td>
</tr>
<tr>
<td>TGFBR1 (TGFβ receptor type 1)</td>
<td></td>
</tr>
<tr>
<td>CXCL8 (interleukin 8)</td>
<td>Immune response</td>
</tr>
<tr>
<td>LOXL4 (lysyl oxidase homolog 4)</td>
<td></td>
</tr>
<tr>
<td>PLAT (tissue type plasminogen activator)</td>
<td>Fibrinolysis/wound healing</td>
</tr>
<tr>
<td>SERPINE2 (glia-derived nexin)</td>
<td></td>
</tr>
<tr>
<td>ITGB3 (integrin β3)</td>
<td>Angiogenesis</td>
</tr>
</tbody>
</table>

Gene expression profile: 8 genes tied to biological processes inherent to metastasis - angiogenesis, blood coagulation, metabolism, cell adhesion and migration

Bellomo et al., A Model Combining Tumor Molecular and Clinicopathologic Risk Factors Predicts Sentinel Lymph Node Metastasis in Primary Cutaneous Melanoma. 2020 JCO-PO (4): 319-334
CP-GEP negative: risk of SLN metastasis is < 5% and patients can safely forgo SLN biopsy

<table>
<thead>
<tr>
<th>T-Stage</th>
<th>NPV</th>
<th>SLNB reduction rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0.98</td>
<td>0.828</td>
</tr>
<tr>
<td>T2</td>
<td>0.95</td>
<td>0.423</td>
</tr>
<tr>
<td>T3</td>
<td>1.00</td>
<td>0.045</td>
</tr>
</tbody>
</table>

False negative rate for this test 1.5%
False negative rate for SLNB is 4.8%
Performance of the CP-GEP Model in Validation Studies

### Prevalence and Performance Metrics

<table>
<thead>
<tr>
<th>T stage</th>
<th>n</th>
<th>Prevalence</th>
<th>NPV</th>
<th>PPV</th>
<th>SLNB reduction rate</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>210</td>
<td>27.5%</td>
<td>90.5%</td>
<td>31.0%</td>
<td>20.0%</td>
<td>92.9%</td>
<td>24.7%</td>
</tr>
<tr>
<td>T1</td>
<td>11</td>
<td>9.1%</td>
<td>100%</td>
<td>N/A</td>
<td>90.9%</td>
<td>0%</td>
<td>90.9%</td>
</tr>
<tr>
<td>T2</td>
<td>94</td>
<td>18.1%</td>
<td>89.3%</td>
<td>21.2%</td>
<td>29.8%</td>
<td>82.4%</td>
<td>32.5%</td>
</tr>
<tr>
<td>T3</td>
<td>70</td>
<td>42.9%</td>
<td>75.0%</td>
<td>43.9%</td>
<td>5.7%</td>
<td>96.7%</td>
<td>7.5%</td>
</tr>
<tr>
<td>T4</td>
<td>35</td>
<td>27.8%</td>
<td>N/A</td>
<td>25.7%</td>
<td>0.0%</td>
<td>100%</td>
<td>25.7%</td>
</tr>
<tr>
<td>T1 &amp; T2</td>
<td>105</td>
<td>17.1%</td>
<td>92.1%</td>
<td>20.9%</td>
<td>36.2%</td>
<td>82.4%</td>
<td>39.8%</td>
</tr>
</tbody>
</table>

### Ongoing Validation Studies US/EU - 2020/21:
- **EU**: pan-European cohort of +3000 samples
- **US**: multi-Institutional cohort of +600 samples

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CP-GEP Model is able to reduce >35% of the SLNB-RR with high NPV for the T1-T2 patients in all three cohorts.

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**References:**
3. Johansson et al. Independent validation study of a CP-GEP model (Merlin Assay) to identify patients with melanoma who can safely forgo sentinel lymph node biopsy. 2021 poster WCM/EADO
# CP-GEP Model comparison to GEP and nomogram

<table>
<thead>
<tr>
<th></th>
<th>31-GEP</th>
<th>CP-GEP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical utility</strong></td>
<td>Identify patients who may safely forgo SLNB and guide closer surveillance/adjuvant therapy decisions</td>
<td>Identify patients who may safely forgo SLNB and guide closer surveillance/adjuvant therapy decisions</td>
</tr>
<tr>
<td><strong>Intended use</strong></td>
<td>Melanoma patients with tumors ≥0.3mm</td>
<td>Any SLNB eligible melanoma patients</td>
</tr>
<tr>
<td><strong>Risk labels</strong></td>
<td>4 risk classes: low risk (1A, 1B), high risk (2A, 2B)</td>
<td>2 risk groups: Low Risk and High Risk</td>
</tr>
<tr>
<td><strong>Technical specifications</strong></td>
<td>▪ Amount: 9 x 5 um FFPE slides</td>
<td>▪ Amount: 10 x 5 um FFPE slides</td>
</tr>
<tr>
<td></td>
<td>▪ Macrodissection: YES</td>
<td>▪ Macrodissection: NO</td>
</tr>
<tr>
<td><strong>Available evidence</strong></td>
<td>▪ &gt;5 US validation studies</td>
<td>▪ Multiple EU and US validation studies</td>
</tr>
<tr>
<td></td>
<td>▪ Multiple prospective studies, but follow-up period is limited (&lt; 5 years)</td>
<td>▪ Prospective trial started Q2 2021</td>
</tr>
<tr>
<td></td>
<td>▪ Not compared with publicly available CP tools</td>
<td>▪ CP-GEP has shown to have superior performance than publicly available CP tools</td>
</tr>
</tbody>
</table>

**For NPVs above 95%:** MIA nomogram achieves SLNB reduction rates up to 35%, CP-GEP achieves SLNB reduction rates up to 60%

**MIA nomogram could not be applied for 19% of patients**
In this group CP-GEP achieved an SLNB reduction rate of 37%

The CP-GEP model that can be applied to all patients achieves a higher SLNB reduction rate than the CP tool.

Bartlett et al. and Varey et al. JCO PO 2020 ([link](#))
Clinical Case Study CP-GEP Low Risk:
62 yo white non-Hispanic male; Mayo Clinic, Jacksonville, FL

<table>
<thead>
<tr>
<th>Dermatology Diagnosis</th>
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<tbody>
<tr>
<td>Lesion (0.9mm) - Biopsy (shave)</td>
</tr>
<tr>
<td>FFPE embedding</td>
</tr>
<tr>
<td>Dermpath: BT=0.9mm, MR-2/mm², Clark=IV</td>
</tr>
<tr>
<td>T-classification: pT1b</td>
</tr>
<tr>
<td>Stage IB</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Surgical Visit</th>
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<tbody>
<tr>
<td>Consultation H&amp;N surgeon</td>
</tr>
<tr>
<td>Lab testing (CBC/Chem)</td>
</tr>
<tr>
<td>NCCN guidelines &amp; SLNB discussed</td>
</tr>
<tr>
<td>Plan: lymphoscintigraphy, WLE (1cm margin)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-Op Visit &amp; Lymphoscintigraphy</th>
</tr>
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<tbody>
<tr>
<td>Medical evaluation by Registered Nurse</td>
</tr>
<tr>
<td>ECG</td>
</tr>
<tr>
<td>Low risk sleep apnea related complications</td>
</tr>
<tr>
<td>Patient medically fit for surgery</td>
</tr>
<tr>
<td>Tc 99m injection</td>
</tr>
<tr>
<td>SPECT-CT imaging</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Surgery Day</th>
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</thead>
<tbody>
<tr>
<td>General anesthesia</td>
</tr>
<tr>
<td>Procedure: WLE on scalp, left SLNB</td>
</tr>
<tr>
<td>Staff: anesthesiologist &amp; assistant, surgeon &amp; assistant</td>
</tr>
<tr>
<td>No complications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology (frozen tissue, permanent sections &amp; IHC)</td>
</tr>
<tr>
<td>Final diagnosis: - no residual melanoma at biopsy site</td>
</tr>
<tr>
<td>- 7 benign lymph nodes identified and melanoma negative</td>
</tr>
<tr>
<td>- SLNB is negative</td>
</tr>
</tbody>
</table>

Day 1
Order CP-GEP

Day 5
Result: CP-GEP Low Risk

Day 7

Day 15

Day 16

Day 21

What Can We Agree On?

• T1 and some T2 melanomas may not need SLNB
  • Especially those with <5% risk of a positive node
• Depends on many or all of these factors being present
  • Age of the patient
  • Certain Breslow thickness/Clark level
  • Mitotic rate, LVI, Ulceration
  • GEP results

Predicting SLNB Status

• CP-GEP Model
  • Ongoing prospective trial with CP factors and GEP to identify patients at low risk of SLNB positivity (<5%)
  • GEP test has been validated at
    • Erasmus Medical Center in Netherlands
      • 36% could have safely avoided SLNB
    • Mayo Clinic, MN
      • 44% reduction in SLNB in T1-T2 melanomas
Summary
Prognostic GEP Testing for Melanoma 2021

• New CP-GEP Model combines clinicopathologic variables and gene expression profiling to identify melanoma patients that can safely forgo a SLNB
  • Potentially reducing SLNB rate by over 80% for T1 and 42% for T2 patients

• Independent validation studies in EU and US show consistent performance of CP-GEP Model

• Ongoing validation studies both in EU and in the US

• Ongoing carefully designed prospective randomized clinical trials
Validation of a 40-gene expression profile test to predict metastatic risk in localized high-risk cutaneous squamous cell carcinoma

• Prognostic test to identify cSCC that can metastasize and may benefit from further intervention and surveillance
• Prospective study from 23 independent centers using FF PE tissue from n=586 cSCC
• GEP developed using a discovery cohort (n=202) and validated in a separate independent cohort (n=324)
• 40 genes were most predictive of SCC metastasis
  • Deep learning used to narrow the genes from ~150 genes

Gene expression profile test to predict metastatic risk of primary cSCC

- Consider in high risk cSCC in any patient with ≥ high risk features
  - Tumor size > 2 cm
  - Depth > 4mm or into the subcutaneous fat
  - Moderately to poorly differentiated
  - Perineural invasion
  - Recurrent tumor
  - Immunocompromised patient
  - Site of prior RXT or chronic inflammation

<table>
<thead>
<tr>
<th>CLASS</th>
<th>RISK</th>
<th>3 Year Metastasis-Free Survival Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LOW Risk</td>
<td>91.4%</td>
</tr>
<tr>
<td>2A</td>
<td>HIGH Risk</td>
<td>80%</td>
</tr>
<tr>
<td>2B</td>
<td>HIGHEST Risk</td>
<td>44%</td>
</tr>
</tbody>
</table>
COVID-19-associated dermatologic manifestations from an international registry of 716 patients from 31 countries

- Morbilliform (35%)
- Chilblain (perniosis)-like (18%)
- Urticarial (16%)
- Vesicular (11%)
- Papulosquamous (10%)
- Retiform purpura (livedo/necrosis) (6.4%)

-Cutaneous COVID-19 manifestations presented simultaneous to or after other COVID-19 symptoms -12% occurred before other COVID-19 signs
Perniosis (Chilblains)-like COVID toes

- Younger patients
- Feet (84%) and hands (32%)
- Pruritic (36%)/painful/burning (71%)
- No prior perniosis history
- Occurred later in the course of disease
  - May not have COVID sx
- % of confirmed COVID-19 lowest in this group
  - +PCR and antibodies often neg
- Associated with less severe disease
- Lasted 7 days (range 3-30d)
Perniosis (Chilblains)-like COVID toes
Acral Retiform Purpura

*Older* patients on the extremities and buttocks

Highly variable presentation—ranging from transient livedo to frank necrosis, *often asymptomatic* (73%)

After other COVID-19 symptoms (91%)

Associated with more *severe* disease (100% hospitalized, 82% with ARDS, 10% mortality)

Pauci-inflammatory thrombogenic vasculopathy

Likely a cutaneous manifestation of a systemic hypercoagulable state

- Elevated d-dimer
- Evidence of systemic coagulopathy
Acral Retiform Purpura

-Viral RNA in the endothelium negative
-Spike glycoprotein and membrane protein expressed within the endothelial cells
Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases

83% of the cutaneous reactions were from Moderna and 17% from Pfizer.

43% of patients with 1st-dose reactions had a 2nd dose recurrence.

The reactions were not serious and resolved spontaneously.

Delayed large local reactions were most common, followed by local injection site reactions, urticarial eruptions & morbilliform eruptions.

Less common reactions included perniosis/chilblains, cosmetic filler reactions, and flares of existing conditions (HSV/VZV, rosacea).

Dermatologic toxicities to immune checkpoint inhibitor therapy: A review of histopathologic features

Immune checkpoint inhibitor therapy has revolutionized cancer treatment

Checkpoint inhibitors are monoclonal antibodies that block cytotoxic T-lymphocyte-associated antigen-4, programmed cell death protein 1 or programmed cell death ligand 1

Checkpoint inhibitors are associated with a range of cutaneous adverse reactions highlighting the complexity of the immune response and the importance of clinical-histopathologic correlation is the accurate and timely recognition of these reactions, allowing for appropriate intervention and patient care

Dermatologic toxicities to immune checkpoint inhibitor therapy:
A review of histopathologic features

- Morbilliform/urticarial eruption
- Eczematous dermatitis
  - Seborrheic dermatitis-like facial eruption
- Psoriasiform dermatitis
  - AGEP, flare of psoriasis
- Neutrophilic dermatosis
  - Sweet syndrome, PyG
- Sarcoidal granulomatous dermatitis
- Interface (vacuolar or lichenoid) dermatitis
  - SJS/TEN, DRESS, SCLE-like, DM-like, TEC, LPP
  - Photosensitivity to UVA
- Immunobullous
  - BP
- Acantholytic/Grover disease
- Vasculitis
- Panniculitis (EN, neutrophilic)
- Alopecia (AA)
Dermatologic toxicities to immune checkpoint inhibitor therapy: A review of histopathologic features

- Acneiform folliculitis, facial cysts, rosacea
- Vitiligo-like leukoderma
  - Regression of melanocytic nevi
- Radiation-associated dermatitis
- Sclerodermoid reactions
- KA/SCC, squamous papillomas
- Pyogenic granulomas

**Pearl**

You need to be familiar with the skin-related toxicities associated with targeted therapies

*Ellis et al. J Am Acad Dermatol 2020; 83:1130-43*
Deep Learning in Dermatopathology

• To date, the majority of studies using AI in DP have been based on whether a diagnosis or feature is present or absent
  • AI useful for diagnosis of very common entities
    • Algorithms have been trained to recognize BCC, DN, & SK at an accuracy of >99%
  • AI can support intraoperative consultation during Mohs surgery
    • A recent study also demonstrated a sensitivity of 100% and specificity of 94% for the detection of BCC in Mohs slides
Deep Learning in Dermatopathology

• AI is in its early stage of development in DP compared to Radiology

• AI may eventually produce a tool capable of triage in DP
  • ↓ turnaround time; prioritizing workload & improving workflow efficiency
    • Most challenging cases identified for ancillary testing or consultation

• AI being evaluated for potential to help in the classification of melanocytic neoplasms reducing interrater discordance in the interpretation of these lesions
Deep Learning in Dermatopathology

• Barrier to AI application in pathology is the lack of digital data

• High cost and disruptive changes in workflow are major factors that prevent laboratories from converting to a digital workflow

• Performance of AI will depend on validity of data sets used
  • Concordance rate among dermatopathologists is poor for atypical melanocytic lesions, MIS and early melanoma. The training data sets need to be concordant.

• Therefore, classification of the myriad of diagnoses in DP and thinking like a dermatopathologist will not be a reality anytime soon
Deep Learning in Dermatopathology

References


Summary

- Dysplastic nevi – to re-excise or not re-excise
- New IHC stains (for MTS, MCC; PRAME; BAP1)
- Molecular era in DP
- Prognostic GEP tests in malignant melanoma and SCC
- COVID-19: cutaneous manifestations & cutaneous reactions to the COVID vaccines
- Cutaneous toxicities to checkpoint inhibitors
- AI in DP
Thank you!

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Comments/Questions

Q & A

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