Diagnostically Challenging Melanocytic Tumors

Memorial Sloan Kettering Cancer Center, NYC
New Jersey, USA
Melanocytic Tumors - Diagnostic Challenges

- Small partial view
- Primary or metastatic melanoma?
- Desmoplastic melanoma or not?
- Benign proliferative nodule or melanoma?
I. Melanoma in situ or junctional nevus?
Melanoma in situ
Melanoma in situ
Clinical Correlation: Melanoma in situ

76M – changing lesion
Melanoma in situ

PRAME

Sox10
What is Your Diagnosis?
What is Your Diagnosis?
What is Your Diagnosis?
What is Your Diagnosis?

A. Melanoma in situ

B. Melanoacanthoma

C. Melanocytic nevus

D. Don’t know yet (“intraepidermal melanocytic proliferation”)
Diagnosis: Traumatized Melanocytic Nevus

- Patient referred with a diagnosis “probable melanoma in situ”
- Clinical findings not typical for MIS
- Repeat biopsy for final diagnosis
Diagnosis: Traumatized Melanocytic Nevus
Ashbury Park, NJ
Stone Pony, Ashbury Park, NJ
Ashbury Park, NJ
The Boss

Watch Bruce Springsteen Join Southside Johnny Onstage in Asbury Park

By MICHÉLE AMABILE ANGERMILLER
II. Primary or Metastatic?
What is Your Diagnosis?

- 51 F with h/o metastatic melanoma
Cytology of tumor cells
What is Your Diagnosis?

A. Bap1-inactivated melanocytoma

B. Primary nodular/dermal melanoma

C. Metastatic melanoma

D. Other
Diagnosis: Melanoma

- BAP1 retained (no loss)
- Atypia and no maturation
- TMR: 6/mm²
- 4+ PRAME
Metastatic melanoma of unknown primary
Clinical History

- Skin nodule present 3 years prior to metastasis
- Treated as probable DF with liquid N2 (not at MSKCC)
- Metastasis at site of lymphatic drainage
Diagnosis: Primary Dermal Melanoma
PDM – a diagnostic challenge for staging

Case Report
Primary Dermal Melanoma: A Rare Clinicopathological Variant Mimicking Metastatic Melanoma

Oriana Simonetti 1,*,1, Elisa Molinelli 1,*, Valerio Brissigotti 1,*, Donatella Brancosini 2, Davide Talevi 3 and Annamaria Offidani 1
Primary Dermal Melanoma

- 11 of 1800 melanoma patients presented with solitary nodule and no associated precursor
- Initially thought to be metastatic
- Unusual high survival rate suggests that they may be primary tumors
Primary Dermal Melanoma

Definition:
- Melanoma in dermis and/or subcutis
- No associated in situ melanoma or nevus

Study:
- 7 cases with mean thickness of 7 mm
- 100% survival (mean FU of 41 months)
Primary Dermal Melanoma

Primary dermal melanoma: clinical behaviour, prognosis and treatment

Christopher G. Harris a, b, Serigne Lo a, c, Tasnia Ahmed a, Richard A. Scolyer a, b, c, d, Peter M. Ferguson a, b, c, d, Rooshdiya Z. Karim b, c, d, Tai Khoa Lam b, Kenneth K. Lee a, Kerwin F. Shannon a, b, c, Andrew J. Spillane a, c, e, Jonathan R. Stretch a, b, c, John F. Thompson a, b, c, Robyn PM. Saw a, b, c, e

Eur J Surg Oncol 2020; 2131 - 39

- 62 PDM (MIA 1978 – 2013)

- Disease-free survival similar to stage I-II controls

- Prognosis much better than for stage IV M1a controls
PDM – Genetically Heterogeneous
Primary Dermal Melanoma

A solitary dermal melanoma nodule is most likely primary, unless there is a known history or other concurrent evidence of melanoma.
What is Your Diagnosis?

- 26 M with nodule on temple
Nevus or Melanoma?
Diagnosis - Melanoma

- Asymmetric pigmentation
- Focal pagetosis
- Cytologic atypia
- Mitoses
- 4+ Labeling for PRAME
Additional Diagnostic Clue

Scar
16 months earlier...
Melanoma associated with a nevus
Excision with neg margins
Current Tumor: Metastatic Melanoma
Metastatic Melanoma
Staging of melanoma – Clinical context matters

• Prior history of melanoma

• Clinical presentation of tumor

• Evidence from other clinical studies and follow-up

• Evidence from ancillary tests, especially molecular studies
Princeton University, Princeton, NJ
III: Desmoplastic Melanoma

• Diagnostic Pitfall
  • Difficult to diagnose clinically
  • Risk for misdiagnosis by pathologist

• Distinct Variant of Melanoma
  • Distinct pathologic features
  • Distinct clinical behavior
DM Pathology – Differential Diagnosis

• DM vs benign fibrosing lesion
  • DM vs scar
  • DM vs dermato- or neurofibroma or other benign nerve sheath tumor
  • DM vs desmoplastic melanocytic nevus (acquired or congenital)

• DM vs non-melanocytic malignant tumor
  • Spindle cell sarcoma with desmoplasia
  • Desmoplastic carcinoma (usually desmoplastic SCC)
What is Your Diagnosis?

86 yo man with pink papule on scalp
What is Your Diagnosis?

86 yo man with pink papule on scalp
Clinical context: Near surgical scar for lentigo maligna

86 yo man with pink papule on scalp
86 yo man with pink papule on scalp

S100P
Clinical context: Near surgical scar for lentigo maligna

86 yo man with pink papule on scalp
Desmoplastic Melanoma

86 yo man with pink papule on scalp
Desmoplastic Melanoma
DM – Confusion with a scar
Desmoplastic Melanoma
What is Your Diagnosis?

Re-excision for melanoma in situ
What is Your Diagnosis?

Sox10
S100P/Sox10-positive cells in scars


S100-Positive Spindle Cells in Scars
A Diagnostic Pitfall in the Re-Excision of Desmoplastic Melanoma

Joe A. Chorny, M.D., and Ronald J. Barr, M.D.

Scar with Sox10/S100-positive cells – not DM
Desmoplastic Melanoma – Diagnostic Pitfall

Pitfalls in the Diagnosis of Malignant Melanoma

Findings of a Risk Management Panel Study

David B. Troxel, MD

Unrecognized Desmoplastic Melanoma
(3 Claims)

More than half of these were shave biopsies (often mis-diagnosed microscopically as dermatofibroma). Most desmo-


Medicolegal Issues with Regard to Melanoma and Pigmented Lesions in Dermatopathology

Amanda Marsch, MD, Whitney A. High, MD, JD. MEnga,b,*

Unrecognized Desmoplastic Melanoma

Suggestion 6: Beware of Desmoplastic Melanoma

Desmoplastic melanoma (DM) is a rare spindle cell malignancy that usually develops on the sun-damaged skin of elderly patients. However, these elderly patients are also predisposed to other spindle cell neoplasms, such as spindle cell squamous carcinoma and atypical fibroxanthoma. Characteristic histopathologic features of DM include spindle-shaped melanocytes, prominent
DM vs Nerve Sheath Tumors

• Neurofibroma

• Schwannoma

• Hybrid Nerve Sheath Tumor
Neurofibroma vs Melanoma

• Histologic Clues for NF-like Melanoma
  • Atypical junctional melanocytic proliferation
  • Lymphoid aggregates
  • Fascicles of spindle cells
  • Nuclear atypia
  • Deep infiltrative growth
  • Involvement of papillary dermis

• Beware of collision scenarios
  • Nevus or melanoma colliding with a neurofibroma
DM vs Desmoplastic Nevus

• Desmoplastic Spitz Nevus
• Sclerosing Blue Nevus
• Other Nevi with Desmoplasia
Findings favoring a desmoplastic nevus

• Clinical
  • Small papule, younger individual, sun-protected site

• Histopathology
  • Small, symmetric, with evidence of maturation
  • Cytology

• Ancillary Studies
  • IHC: Melan-A, p16
  • Molecular: mutation profile
The 2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma

Detailed Analysis of 9 Distinct Subtypes Defined by Their Evolutionary Pathway

David E. Elder, MB ChB, FRCPA; Boris C. Bastian, MD, PhD; Ian A. Cree, MB ChB, PhD, FRCPATH; Daniela Massi, MD, PhD; Richard A. Scolyer, MD, FRCPA, FRCPATH

<table>
<thead>
<tr>
<th>Table 1. Classification of Melanoma (Modified From 2018 WHO Classification)</th>
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<tbody>
<tr>
<td>A. Melanomas typically associated with CSD</td>
</tr>
<tr>
<td>Pathway I. Superficial spreading melanoma/low-CSD melanoma</td>
</tr>
<tr>
<td>Pathway II. Lentigo maligna melanoma/high-CSD melanoma</td>
</tr>
<tr>
<td>Pathway III. Desmoplastic melanoma</td>
</tr>
<tr>
<td>B. Melanomas not consistently associated with cumulative solar damage (no CSD)</td>
</tr>
<tr>
<td>Pathway IV. Spitz melanomas</td>
</tr>
<tr>
<td>Pathway V. Acral melanoma</td>
</tr>
<tr>
<td>Pathway VI. Mucosal melanomas</td>
</tr>
<tr>
<td>Pathway VII. Melanomas arising in congenital nevi</td>
</tr>
<tr>
<td>Pathway VIII. Melanomas arising in blue nevi</td>
</tr>
<tr>
<td>Pathway IX. Uveal melanoma (not considered further in this review)</td>
</tr>
<tr>
<td>C. Nodular melanoma (may occur in any or most of the pathways)</td>
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Abbreviation: CSD, cumulative solar damage.
DM – Clinical Behavior

• Local persistence/recurrence more common

• Regional node metastasis less common

• Survival advantage among thick melanomas
DM – Local Recurrence

• Anatomic site (wide clearance difficult in H&N region)

• Positive margins can be difficult to see

• Perineural invasion
Desmoplastic Melanoma: SLN Biopsy

- 12 patients with desmoplastic melanoma
- SLN biopsies negative
Desmoplastic Melanoma – SLN Biopsy

27 patients with pure DM: Not a single SLN was positive
Different Data from University of Michigan

Desmoplastic and Neurotropic Melanoma
Analysis of 33 Patients with Lymphatic Mapping and Sentinel Lymph Node Biopsy

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Douglas R. Fullen, M.D.1,2
Lori Lowe, M.D.1,2
Timothy S. Wang, M.S.2
Jennifer L. Schwartz, M.D.2
Vincent M. Cimino, M.D.3
Vernon K. Sondak, M.D.3
Timothy M. Johnson, M.D.2,4

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4 Department of Otolaryngology, University of Michigan Medical Center, Ann Arbor, Michigan.

BACKGROUND. Desmoplastic and neurotropic melanoma (DNMM) occasionally metastasizes to regional lymph nodes and extranodal sites. The value of sentinel lymph node biopsy (SLNB) has not been demonstrated clearly for patients with DNMM. The authors report on the utility of SLNB in the management of patients with DNMM.

METHODS. The authors identified 33 patients with DNMM who were seen during a 5-year period in their institution who underwent lymphatic mapping and SLNB. Clinical and histopathologic data were reviewed.

RESULTS. Thirty-three patients with DNMM underwent SLNB (mean Breslow depth, 4.0 mm; median, 2.8 mm). There were 25 male patients and 8 female patients with a median age of 61 years (range, 31–86 years). Fifty-two percent of tumors presented in the head and neck region, and 24% were associated with lentigo maligna. Four of 33 patients (12%) without clinical evidence of metastatic disease who underwent SLNB had at least 1 positive sentinel lymph node. No additional positive lymph nodes were found in subsequent therapeutic regional lymphadenectomy in any of these four patients.

CONCLUSIONS. SLNB detected subclinical metastases of DNMM to regional lymph nodes. SLNB at the time of resection can provide useful information to guide early treatment and, coupled with lymphadenectomy in positive patients, may limit tumor spread and prevent recurrence at the draining lymph node basin. Cancer 2004;100:598–604. © 2003 American Cancer Society.

4/33 patients with positive SLN
These tumors look different...

FIGURE 5. Desmoplastic and neurotropic melanoma from Patient 3 showed a small population of conventional epithelioid melanoma cells (asterisk and inset A) in the upper part of the tumor and atypical spindle cells invading the deep dermis accompanied by prominent desmoplasia (inset B).

FIGURE 6. Desmoplastic and neurotropic melanoma arising in acral lentigious melanoma from the foot of Patient 4 showed highly atypical spindle melanocytes infiltrating the dermis (arrowheads in inset A). Tumor cells displayed neurotropism surrounding and invading nerve twigs in deep dermis (arrowheads in inset B).
Metastases with Melan-A-positive epithelioid cells

**FIGURE 5.** Desmoplastic and neurotropic melanoma from Patient 3 showed a small population of conventional epithelioid melanoma cells (asterisk and inset A) in the upper part of the tumor and atypical spindle cells invading the deep dermis accompanied by prominent desmoplasia (inset B).

**FIGURE 6.** Desmoplastic and neurotropic melanoma arising in acral lentiginous melanoma from the foot of Patient 4 showed highly atypical spindle melanocytes infiltrating the dermis (arrowheads in inset A). Tumor cells displayed neurotropism surrounding and invading nerve twigs in deep dermis (arrowheads in inset B).

**FIGURE 7.** One of a few clusters of metastatic epithelioid melanoma in the lymph node parenchyma from Patient 5 was found to express melan-A.

**FIGURE 8.** In the sentinel lymph node from Patient 4, a few clusters of melan-A positive, atypical epithelioid cells were identified in the parenchyma and perinodal areas, consistent with metastatic melanoma.
Pure vs mixed vs non-desmoplastic Melanoma

Solid spindle cell  Combined (mixed) DM  Pure DM
Pure Desmoplastic Melanoma
Pure Desmoplastic Melanoma
Mixed Desmoplastic Melanoma
Mixed Desmoplastic Melanoma
Mixed Desmoplastic Melanoma

89 M, Scalp
Mixed Desmoplastic Melanoma

Cell-poor stroma-rich

Cell-rich stroma-poor
<table>
<thead>
<tr>
<th>Study</th>
<th>Median thickness (mm)</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Positive SLNB association with DFS, MSS and OS</th>
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<tbody>
<tr>
<td>Jaroszewski 2001</td>
<td>6.5(^a)</td>
<td>12</td>
<td>0 (0%)</td>
<td>–</td>
</tr>
<tr>
<td>Gyorki 2003</td>
<td>2.2</td>
<td>24</td>
<td>0 (0%)</td>
<td>–</td>
</tr>
<tr>
<td>Su 2004</td>
<td>2.8</td>
<td>33</td>
<td>4 (12.1%)</td>
<td>–</td>
</tr>
<tr>
<td>Livestro 2005</td>
<td>2.6</td>
<td>25</td>
<td>2 (8%)</td>
<td>–</td>
</tr>
<tr>
<td>Pawlik 2006</td>
<td>2.9</td>
<td>65</td>
<td>4 (6.2%)</td>
<td>3/19 (15.8%)</td>
</tr>
<tr>
<td>Posther 2006</td>
<td>4.4(^a)</td>
<td>12</td>
<td>0 (0%)</td>
<td>–</td>
</tr>
<tr>
<td>Thelmo 2006</td>
<td>3.9(^a)</td>
<td>16</td>
<td>0 (0%)</td>
<td>–</td>
</tr>
<tr>
<td>Cummins 2007</td>
<td>2.3</td>
<td>15</td>
<td>1 (6.7%)</td>
<td>–</td>
</tr>
<tr>
<td>Maurich 2009</td>
<td>1.9 MDM</td>
<td>100</td>
<td>9 (9%)</td>
<td>7/51 (13.7%)</td>
</tr>
<tr>
<td>Murali 2010</td>
<td>2.1 PDM</td>
<td>252</td>
<td>17 (6.7%)</td>
<td>11/129 (8.5%)</td>
</tr>
<tr>
<td>Wasif 2011</td>
<td>3.0(^a)</td>
<td>505</td>
<td>14 (2.8%)</td>
<td>–</td>
</tr>
<tr>
<td>Mohebati 2012</td>
<td>6.1(^a)</td>
<td>21</td>
<td>0 (0%)</td>
<td>0/7 (0%)</td>
</tr>
<tr>
<td>Eppsteiner 2012</td>
<td>3.5</td>
<td>165</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Broer 2013</td>
<td>3.9(^a)</td>
<td>22</td>
<td>4 (18.2%)</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>Egger 2013</td>
<td>2.6</td>
<td>47</td>
<td>8 (17.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Han 2013</td>
<td>3.7</td>
<td>205</td>
<td>28 (13.7%)</td>
<td>15/61 (24.6%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>1519</td>
<td>99 (6.5%)</td>
<td>38/275 (13.8%)</td>
</tr>
</tbody>
</table>

\(^a\) Mean.
we would not recommend SLN biopsy in pure desmoplastic melanoma
CASE STUDY

The utility of SOX10 in mixed type desmoplastic melanoma with lymph node metastasis of the spindle cell component: A cautionary tale of inattentional blindness

Ahmed Shah MD, MSc | Katelynn Campbell MD | Allison Osmond MD, MSC, FRCPC

CAUTION!

DM: Use S100P or Sox10 for SLN analysis
Survival Advantage for Desmoplastic Melanoma Among $\geq 4$ mm Thick Melanomas

$P=0.004$

Survival Advantage for Pure Desmoplastic Melanoma

- 119 pDM vs 2272 CM
- Pure DM had better MSS
- “Patients with pDM had half the chance of melanoma-specific death”
Representativeness of initial skin biopsies showing pure desmoplastic melanoma: implications for management

R. V. Rawson\textsuperscript{1,2,3,4}, I. A. Vergara\textsuperscript{1,2,5}, J. R. Stretch\textsuperscript{1,2,6}, R. P. M. Saw\textsuperscript{1,2,6}, J. F. Thompson\textsuperscript{1,2,6}, S. N. Lo\textsuperscript{1}, R. A. Sclyer\textsuperscript{1,2,3,4,5}, K. J. Busam\textsuperscript{7}

- 91/101: Biopsy and excision concordant for pure DM
- 10/101: Changed to mixed DM upon review of excision
What is your diagnosis?

70F, cheek – r/o cyst, foreign body, scar
Mixed Desmoplastic Melanoma
CANCER DISCOVERY

Published in final edited form as:

**Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway**

A. Hunter Shain1,2,3, Maria Garrido1,2,3, Thomas Botton1,2,3, Eric Talevich1,2,3, Iwei Yeh1,2,3, J. Zachary Sanborn4, Jongsu Chung5, Nicholas J. Wang6,7, Hojabr Kakavand8,9, Graham J. Mann8,9, John F. Thompson8,9,10, Thomas Wiesner11, Ritu Roy12, Adam B. Osheroff12, Alexander Gagnon1,2,3, Joe W. Gray4,7, Nam Huh5, Joe S. Hur13, Klaus J. Busam14, Richard A. Scolyer8,9,16, Raymond J. Cho5,16, Rajmohan Murari14,16,16, and Boris C. Bastian1,2,3,16

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**Desmoplastic Melanoma Carries High Mutation Burden**

DOI: 10.1158/2159-8290.CD-15-134 Published November 2015
High response rate to PD-1 blockade in desmoplastic melanomas

Zeynep Eroglu1,2, Jesse M. Zaretsky3, Siwen Hu–Lieskovszky4, Dae Won Kim2,3, Alain Algazi4, Douglas B. Johnson7, Elizabeth Liniker5, Ben Kong5, Rodrigo Munhoz6,9, Suthee Rapisiwong6, Pier Federico Gherardini9, Bartosz Chmielowski1, Xiaoyan Wang1, I. Peter Shintaku1, Cody Wei1, Jeffrey A. Sosman1,2, Richard W. Joseph1, Michael A. Postow8,9, Matteo S. Carlino6,7,11, Wen-Jen Hwu1, Richard A. Scolyer6,13,14, Jane Messina2, Alistair J. Cochran1, Georgina V. Long6,13,15 & Antoni Ribas3

- 60 patients with advanced DM treated with anti PD-1/PD-L1
- Tumor response to treatment in 42/60 patients
- 14/17 tumors had NF1 mutations
- IHC: More PD-L1-positive cells and CD8+ T-cells in DM

Nature 2018; 553: 347 - 350
IV: Melanoma associated with congenital nevi

- Risk for melanoma: approx 1%
- Risk for melanoma in giant congenital nevus: 10%
Melanoma of small/medium congenital nevus

- Usually after puberty
- Often at edge of CMN
- Usually a/w melanoma in situ

Betti et al. J of Dermatol 2000;27:583-590 (mean age when MM develop = 41)
Melanoma of giant congenital nevus

- Often large
- Typically unassociated with epithelia (no melanoma in situ)
Diagnostic Challenge: Proliferative Nodules

- Often appear in the neonatal period
- They can be large & atypical

Kerl et al. Mel Res 2001;11:S56)
Benign Proliferative Nodule
Phenotypes of proliferative nodule

- Nevoid melanoma-like
- Blue Nevus/PEM-like
- Spitzoid/Bapoma-like
- Small cell/blastic features
- Mesenchymal
Proliferative Nodule or Melanoma?
6 wk Baby with nodules in CMN
Benign Proliferative Nodule
IHC for H3K27me3
IHC for H3K27me3

Proliferative Nodule

Melanoma
Melanoma arising in a large CMN
Melanoma arising in a large CMN

Nevus

Melanoma
Proliferative Nodule vs Melanoma

**Proliferative Nodule**
- **Clinical**
  - Relatively small, non-ulcerated
- **Pathology**
  - Organized, differentiated
  - Circumscribed
  - Atypia and mitoses variable
  - Tends to blend with nevus
- **Ancillary Studies**
  - No or whole chromosome aberrations
  - IHC for H3K27me3 (positive)

**Melanoma**
- **Clinical**
  - Large, ulcerated
- **Pathology**
  - Infiltrative
  - Malignant cytology, frequent mitoses
  - Undifferentiated, transdifferentiated
  - Tends to be very different from nevus
- **Ancillary Studies**
  - Segmental copy number aberrations
  - IHC for H3K27me3 (negative)
Ancillary Studies for Diagnosis: Cytogenetics

Genetic Changes in Neoplasms Arising in Congenital Melanocytic Nevi

Differences Between Nodular Proliferations and Melanomas

Boris C. Bastian,†‡ Jessica Xiong,† Ilona J. Frieden,* Mary L. Williams,* Pauline Chou,† Klaus Busam,‡ Dan Pinkel,‡ and Philip E. LeBoit†‡

From the Departments of Dermatology* and Pathology† and the University of California at San Francisco Comprehenive Cancer Center‡ University of California at San Francisco, San Francisco, California; the Department of Pathology§ Children's

quent numerical chromosomal aberrations in atypical nodular proliferations arising in CMN identifies these as clonal neoplasms with a genomic instability consistent with a mitotic spindle checkpoint defect. This difference compared to the aberration pattern found in melanoma might explain their more benign clinical behavior and may be of diagnostic value in ambiguous cases. (Am J Pathol 2002, 161:1165–1169)

Kinsler et al BJD 2017;176:1143
Test Limitations

Metastatic Melanoma in Association With a Giant Congenital Melanocytic Nevus in an Adult: Controversial CGH Findings

Salma Machan, MD,* Ana M. Molina-Ruiz, MD,* Maria J. Fernández-Aceñero, MD,† Beatriz Encabo, MD,† Philip LeBoit, MD,‡ Boris C. Bastian, MD,‡ and Luis Requena, MD*

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• Colleagues at MSKCC

• Many collaborators at other institutions

• My family
Thank You!

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