Patterns and mechanisms of inflammatory skin conditions: the pathologist’s survival kit

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BAHRAIN, APRIL 2017
Basic Elements of Lesions

- Toxic (Direct/Indirect)
- Vascular
- Inflammatory (immune-mediated or not)
- Trophic

- Inflammation
  - Vascular component
  - Cellular component
  - Regeneration/reparation
  - Intracellular mechanisms
Cell damage – oncosis
Cell damage – cytopathic
Inflammatory – Extracellular/vascular
Hyperplastic reaction
Combined
Inflammatory – cellular

- Toxic (Direct/Indirect)
- Vascular
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- Inflammation
  - Vascular component
  - Cellular component
  - Regeneration/reparation
  - Intracellular mechanisms

Time & Intensity
Repair
Injury

Patterns
Biological Basis of Elementary Lesions

- **Cellular response**
  - Cell perpetuation pathway
  - Cell differentiation pathway
  - Activation of “default” pathway – cell death

- **Tissue effects**
  - Parenchyma and stroma interactions

- Combination of findings depending on the primary damage target
## Biological Processes and Pathology

<table>
<thead>
<tr>
<th>Primary Biological Process</th>
<th>General Pathology</th>
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| Increased keratinocyte turnover | Hyperplastic changes  
Lack of full cell differentiation  
Relative increase of cell loss |
| Decreased keratinocyte turnover | Relative atrophy  
Full cell differentiation  
Decreased cell loss |
| Inflammation | Vascular changes and permeability  
Cellular infiltrate  
Cell damage (stroma, vessels, epithelia) |
| Cell damage | Reversible  
Irreversible  
Regeneration and reparation |
Psoriasiform Acanthosis

Dermatophytosis
Psoriasis
Seborrheic dermatitis
Allergic contact / nummular dermatitis
PRP
Secondary syphilis
Scabies, Norwegian type
MF
Psoriasiform Dermatitis

Neutrophils within parakeratosis
Superficial perivascular dermatitis

Psoriasis
Irregular Epidermal Hyperplasia

Pseudoepitheliomatous hyperplasia
Suppurative granulomatous dermatitis

Deep mycosis, atypical mycobacteria
Markedly Thinned Epidermis

- Dermatomyositis/DLE
- DLE
- GVHD
- LP, atrophic
- LP-like keratosis
- Porokeratosis
- Lichen sclerosus
- Degos’ disease
Interface Dermatitis

- Leukocyte infiltration of the dermis
- Vacuolar change of basilar epidermis
- Papillary dermal melanophages
- Necrosis of keratinocytes
- AKA: lichenoid tissue reaction pattern, vacuolar interface dermatitis
Lichenoid Interface Dermatitis

- Wedge-shaped hypergranulosis
- Lichenoid infiltrate

Lichen planus
Vacuolar Interface Dermatitis

- Necrotic keratinocytes
- Vacuolar alteration
- Lichenoid inflammation
- Superficial perivascular lymphohistiocytic

Erythema Multiforme
Spongiotic Dermatitis

Spongiosis around acrosyringia

Miliaria rubra
Eosinophilic Spongiosis

BP/HG, urticarial
Allergic dermatitis
Pemphigus vulgaris, urticarial
Arthropod assault
Dermatophytosis
Incontinentia pigmenti, vesicular
Toxic erythema of newborn
Lymphocytic Infiltrate

DLE, tumid
Pernio
PLE
Insect bite
Erythema figuratum
Perivascular Lymphoplasmacytic Infiltrate

Acrodermatitis chronica atrophicans
Erythema chronicum migrans
Secondary syphilis
Necrobiosis lipoidica
Morphea
# Exocytosis vs. Epidermotropism

<table>
<thead>
<tr>
<th>EXOCYTOSIS</th>
<th>EPIDERMOTROPISM</th>
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<tbody>
<tr>
<td>Random through epidermis to surface</td>
<td>Lower third/half epidermis</td>
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<tr>
<td>Spongiotic tissue reaction</td>
<td>Tendency to aggregate</td>
</tr>
<tr>
<td>Inflammatory processes</td>
<td>No/little spongiosis</td>
</tr>
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<td>Feature of MF</td>
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</tbody>
</table>
Superficial and Deep Inflammation

Light reaction
Lymphoma
Leprosy
Lues
Lichen striatus
Lupus erythematosus
Lipoidica (necrobiosis)
Lepidoptera (+ other arthropods)

Dermatophyte
Reticular erythematous mucinosis
Urticarial stages (BP)
Gyrate erythemas
Scleroderma (localized)
Drug reactions

8Ls + DRUGS
Nodular Dermatitis

Germinal centers in a dense nodular or diffuse infiltrate

Delayed hypersensitivity reaction
Abnormal Lymphocytes in Mixed Cell Infiltrate

- Tick bite reaction
- Herpesvirus
- Dermatophytosis
- Ruptured molluscum
- Kikuchi’s disease
- Gianotti-Crosti
- Lymphomatoid papulosis
- MF
Dense Mixed Inflammation

Granuloma faciale / Erythema elevatum diutinum

Nodular scabies

Tick bite reaction
Subcorneal Pustule

- Dermatophytosis
- Candidiasis
- Impetigo
- Suppurative infundibulitis
- Pemphigus foliaceus
- Pustular psoriasis
- Prurigo pigmentosa
Papillary Micro-abscesses

- DH / linear IgA dermatitis, drug eruptions
- Acquired EB
- DLE
- Bullous LE
- LCC vasculitis
Interstitial Neutrophils in Reticular Dermis

- Urticaria
- Cutis laxa
- DH / linear IgA dermatitis
- Bullous LE
- Fixed drug eruption
- Cellulitis
- Flea bite
- Pustular infundibular dermatitis
- LCC vasculitis
- Sweet’s / PG
- Lymphomatoid papulosis
Cytopathic Dermatitis

Acantholytic separation
Multinucleated epithelial giant cells

Herpesvirus infections
Ballooning

EM
Fixed drug eruption
Mucha-Haberman
Prurigo pigmentosa
Hand-foot-mouth disease
Herpesvirus
Milker’s nodule/orf
Irritant contact dermatitis
Burn
Fibrosing Dermatitis

- Thinned epidermis
- Thickened edematous / sclerotic papillary dermis
- Underlying mononuclear infiltrate

Lichen sclerosus
Fibrosing Dermatitis

Decreased number of adnexal structures

Fibrosing inflammatory of neoplastic conditions
Elements of Pattern Recognition

- With/without epidermal changes
  - Spongiotic, interface, hyperplastic, atrophic

- Distribution of inflammatory infiltrate
  - Topography – Superficial vs. superficial & deep
  - Microanatomy – Perivascular, interstitial, nodular, diffuse

- Type of inflammatory infiltrate
  - Mononuclear – Lymphocytes ± histiocytes
  - Mixed – Mono- and polymorphonuclear
  - Polymorphonuclear ± eosinophils
Approach to Microscopic Diagnosis

Inflammatory Conditions with Epidermal Alteration

- Psoriasiform dermatitis
  - Lichenoid type
  - Vacuolar type
- Interface dermatitis
- Spongiotic dermatitis
  - Conventional
  - Eosinophilic
  - Follicular
  - Miliarial
- Vesicobullous conditions
  - Intraepidermal
    - Subcorneal
    - Stratum spinosum
    - Suprabasilar
  - Subepidermal
    - Junctional
    - Dermolytic
Inflammatory Conditions with Epidermal Alteration

Psoriasiform dermatitis
- Interface dermatitis
  - Lichenoid type
  - Vacuolar type
- Spongiotic dermatitis
- Vesicobullous conditions
  - Intraepidermal
  - Subepidermal
- Cytopathic Dermatitis
  - Intraepidermal
  - Subepidermal

Psoriasiform dermatitis

Lichenoid dermatitis

Vacuolar dermatitis

Spongiotic dermatitis

Cytopathic dermatitis

Intraepidermal bullous dermatitis

Subepidermal bullous dermatitis
Approach to Microscopic Diagnosis (2)
Lesions by Topography

Adnexal structures
- Folliculitis and perifolliculitis
- Follicular lesions with alopecia

Subcutaneous soft tissue
- Panniculitis
Inflammatory conditions without epidermal alterations

Dermal/subcutaneous inflammatory process

Skin appendages disorders
  - Folliculitis/perifolliculitis
  - Alopecia

Panniculitis/fasciitis
  - Septal
  - Lobular

Folliculitis
Perifolliculitis
Lobular panniculitis
Septal panniculitis
Perifolliculitis

Peri-infundibular and perifollicular fibroplasia

Long-standing perifolliculitis (traction alopecia, LPP)
Non-scarring Alopecia

Catagen or telogen follicles
NO inflammatory infiltrate
Other findings:
◦ Plucked hair
◦ All telogen hairs

Common baldness, telogen effluvium, trichotillomania
 Mostly Septal Panniculitis

Miescher’s radial granuloma
  ◦ Linear spaces containing lipids
  ◦ Tiny collections of neutrophils
  ◦ Palisading histiocytes

Erythema nodosum
Mostly Lobular Panniculitis

Arteritis
Fat necrosis
Suppuration
Granulomas
Fibrosis

Nodular vasculitis
“Cell-Poor” Subepidermal Blister

Suction blister
Gas gangrene
Porphyria cutanea tarda
Bullous dermatosis of hemodialysis
Bullous amyloid
Blister above scar
Hypoxemia blister
Electric current
Second-degree burn
Bullous pemphigoid
EB
Darier’s disease, systematized epidermal nevus
Grover’s disease
Porokeratosis
Solar keratosis
Antigen Presentation, Inflammation & Hypersensitivity
Antigen Processing
Inflammatory and Cellular Response after Injury
INACTIVATION

Soluble Ag-Ab complexes
Neutralization of Ag

CELL-MEDIATED CYTOTOXICITY

ADCC/increased cell adhesion
Ag release

DELAYED HYPERSENSITIVITY

Ag-Ab complex transfer
Mediator release – Necrosis

GRANULOMATOUS REACTION

Poorly degradable Ag
Release of soluble Ag-Ab complexes

C’ activation
Increased cell adhesion
Vasopermeability

ANAPHYLACTIC

IMMUNE COMPLEX

CYTOTOXIC

Soluble complexes

Mediator release – Adhesion

Mediator release

Poorly degradable Ag
Interstitial Granulomatous Infiltrate

- Granuloma annulare
- Dermatofibroma
- Interstitial granulomatous dermatitis
- Necrobiosis lipoidica
- MF, interstitial type
- MF (granulomatous slack skin)
Palisaded Granuloma

Granuloma annulare
Gout
Rheumatoid nodule
Interstitial granulomatous dermatitis
Necrobiosis lipoidica
Necrobiotic xanthogranuloma
Sarcoidal granulomas

**Sarcoidal granulomatous pattern**
- Cohesive epithelioid histiocytes
- Few or no lymphocytes

Sarcoidosis, hallogenoderm
Tuberculoid granulomas

- Tuberculoid granulomatous pattern
  - Collections of epithelioid histiocytes
  - Lymphocytes and plasma cells

Mycobacterial infections, leishmania, subcutaneous sarcoid
Suppurative granulomas

Suppurative granulomatous inflammation
- Neutrophils and necrotic debris
- Histiocytes
- Few or no lymphocytes

Rupture infundibular cyst, sporotrichosis, dermatophytes
Vasculitis

Neutrophils, nuclear dust and fibrin in small blood vessel walls

Leukocytoclastic vasculitis
Vasculitis

Neutrophils, nuclear dust and fibrin in small blood vessel walls
Thrombi within their lumina

Septic vasculitis
Psoriasiform Dermatitis
Vacuolar Interface Dermatitis

Interface Dermatitis with perivascular infiltrate
Lichenoid Interface Dermatitis
Spongiotic Dermatitis
Superficial PV Dermatitis
Nodular Dermatitis
Granulomatous Dermatitis
Fibrosing Dermatitis
Mostly Septal Panniculitis
Mostly Lobular Panniculitis
Pathology for ADR Evaluation

Confirmation of Drug Etiology
- Eosinophils
- Necrotic keratinocytes
- Vascular changes
  - Endothelial prominence
  - Hyperpermeability

Patterns and Mechanisms
- Exanthematous
- Extrinsic vascular
- Spongiotic
- Vesiculo-spongiotic
  - Intrinsic vascular ± granulomas
  - Vesiculopustular
  - ± lichenoid or psoriasiform component

Prognosis/Activity
- Extension of necrosis: Confluent or not
- Neutrophilic exocytosis: Isolated / Pustular
- Vascular damage: IVR, vasculitis
- Extension of inflammation: PV, interstitial, nodular, diffuse
Patterns: Common Basic and Secondary

**Exanthematous**
- Commonest pattern
- Basic profile

**Psoriasiform**
- Chronicity
- Relative low risk
- Common as secondary pattern
- Certain drugs if pseudoepitheliomatous

**Lichenoid**
- Chronicity
- Relative low risk
- Common as secondary pattern
Epithelial Damage and Necrosis

- **Basal cells**
  - Isolated, cytotoxic
  - Barrier effect maintained

- **Multifocal**
  - Clustering, cytotoxic
  - Barrier effect maintained

- **Confluent**
  - Multifactorial
  - Barrier effect lost
Vascular Changes and Damage

Perivascular

Basic profile

IVR

Permeability
Minor vessel wall damage

Vasculitis

Permeability
Major vessel wall damage
Neutrophilic Activity

Perivascular

Basic profile

Single cell exocytosis

Spongiosis
No keratinocyte damage/necrosis

Pustular

Spongiosis
With keratinocyte damage/necrosis
Infiltrate Extension

PV + Interstitial
Low grade progressive

Nodular
Severe

Diffuse
Severe & Tissue Damaging

Basic - Perivascular
Type I Hypersensitivity
IgG4-mediated Reactions
Inflammatory Skin Lesions

- Patterns are the result of the interaction of injury agents and tissue response, modulated in intensity and time.

- Elementary lesions will depend on:
  - basic epidermal reaction (based on cellular turnover and maturation),
  - vascular and cellular inflammatory components,
  - types of cells, and
  - distribution of cells (topography and microanatomy).

- Activity should be evaluated from target damage (epithelial necrosis, vasculitis), exocytosis (neutrophilic), and density of infiltrate.

- Morphological and clinico-pathologic correlation should be included in the conclusion.