Self-assessment test handout
Poznan, December 1-3, 2016

Wojciech Biernat MD PhD, Cases 1-6

Case 1
An 85-year-old man presented with a tumor of the left buttock. The correct diagnosis is:

C. Carcinoma in a poroid sebaceoma
The tumor presents two separate components. Subepidermally there is a nested basaloid proliferation of oval cells that focally show sebaceous differentiation and poroid-like structures. This may be consistent with sebaceoma showing ductal differentiation, but ductal (poroid) structures are also visible in the second component presenting infiltrative growth pattern and having features of ‘squamoid’ carcinoma. Altogether the tumor would be more consistent with the diagnosis of carcinoma (porocarcinoma) arising in a poroid sebaceoma.

Cylindroma presents with characteristic jigsaw-puzzle arrangement of tumor nests composed of two cell types: larger, pale ones at the centre and dark at the periphery of aggregations. The tumor is well delineated and usually horizontal to the skin surface, whereas in cylindrocarcinoma this symmetry is lost due to development of carcinomatous component showing architectural (infiltrative growth) and cytological features of malignancy.

Basal cell carcinoma presents basaloid morphology with peripheral palisading of cylindrical cells in the nests. These cells do not show frank differentiation in the centre of the aggregates although uncommonly trichohyalin formation, immature sebocytes and follicular papillae may be seen.

Tricholemmoma is a benign tumor that contains bulbous follicular proliferation of pale and clear cells. Peripherally, these cells form palisade-like arrangement, whereas in the centre keratinization and squamous eddies formation may occur.

Case 2
A 53-year-old female presented with a tumorous infiltrates of the right leg. The diagnosis is:

D. Subcutaneous panniculitis-like T-cell lymphoma
The lymphoma involves the subcutis with pleomorphism of the lymphocytes. The neoplastic cells presents characteristic rimming of the lipocytes. They showed the phenotype: CD3+, CD8+, CD4-, CD56-, TIA1+, and CD20-.

The main differential is lupus profundus. It characteristically exhibits infiltrates of plasma cells, reactive lymphoid follicles, lymphocytic vasculitis, and eosinophilic hyalinization of the fat, with a distinctive honeycomb-like appearance. Erythema nodosum is a predominantly septal panniculitis, with lymphocytes, histiocytes, neutrophils, and/or eosinophils involving the interlobular septae of the pannus. Multinucleated giant cells may appear in older lesions, without caseation, forming Miescher granulomas. Erythema induratum s a predominantly lobular panniculitis, with mixed inflammatory infiltrate often ulcerating, containing caseation and signs of vasculitis. Extranodal NK/T-cell lymphoma, nasal type, typically involves dermis and the subcutis. It shows peculiar angiocentric behavior. The phenotype also differs as it is CD56-positive and EBV driven malignancy without CD8 expression.
Case 3
A 65-year-old female presented with a tumor of the left leg. The correct diagnosis is:

B. **Primary mucinous carcinoma of the skin**
The diagnosis of primary mucinous carcinoma of the skin requires immunophenotyping (TTF1 for pulmonary, CDX2 or CK20 for colorectal) but also clinical metastatic work-up to exclude extracutaneous primary. Phenotype of these malignancies (*lung, breast and GI tract*) may not be completely reliable, e.g. GCDFP15 or mammaglobin may be shared by breast cancer and skin primary. *Malignant mixed tumor* shows remnants of chondroid myxoid or osteoid stroma that contain polygonal or plasmacytoid tumor cells.

Case 4
A 58-year-old female presented with an occipital tumor. The diagnosis is:

A. **Syringocystadenoma with in situ apocrine adenocarcinoma**
The tumor shows focally unequivocal component of syringocystadenoma: papillae are covered by bilayered epithelium with cylindrical cell on the surface and smaller basaloid at the base. The papillae contain numerous plasma cells in the stroma. In a portion of the lesion extensive squamous metaplasia occurs together with exuberant fibroblastic proliferation. In continuity with the papillae there is progressing cellular atypia in the deep seated glandular elements of the tumor in the dermis that resemble ductal carcinoma in situ of the breast. No infiltrative component was identified *Papillary (digital) adenocarcinoma* is a malignant tumor that is composed of papillary protrusions into cystic spaces, that presents high-grade morphology. *Adenosquamous carcinoma* is a malignancy that has features of squamous cell carcinoma and areas with true glandular differentiation. *Carcinoma developing in nevus sebaceous* has remnants of the nevus sebaceous, that in postpubertal individuals demonstrates acanthotic and papillary proliferation of otherwise typical epidermis and sebaceous hyperplasia in the dermis. *Basal cell carcinoma* is a germinative cell-derived malignancy composed of basaloid cell proliferation with various architectural presentations (lobules, cords, columns, etc.). Artifactual separations between tumor aggregates and stroma are typical. The surrounding stroma may also show various changes (e.g. fibromucinous).

Case 5
A 57-year-old male with a nodule of the back. The diagnosis is:

A. **Trichoblastic basal cell carcinoma**
This tumor is composed of basaloid cell with similar presentation of cell nuclei. Artifactual separations between tumor aggregates and stroma are typical. The surrounding stroma may also show various changes (e.g. fibromucinous). *Squamous cell carcinoma*, even the basaloid subtype shows lesser degree of peripheral palisading and lacks fibromucinous change of the stroma. *Trichoolemmoma* is a benign tumor that contains bulbous follicular proliferation of pale and clear cells. Peripherally, these cells form palisade-like arrangement, whereas in the centre keratinization and squamous eddies formation may occur. *Microcystic adnexal carcinoma* is composed of small cornifying cysts at the superficial portion with solid aggregates and glandular elements in the deeper portion of the tumor. *Adenoid cystic carcinoma* is a tumor composed of cribriform aggregates tubules made of basaloid cells containing mucin spaces and eosinophilic membranes around tumor nests.
Case 6
A 25-year-old male presented with a nodular infiltrates of the right buttock and inguinal region. The correct diagnosis is:

D. Granulomatous slack skin
The diffuse infiltrate consists of small lymphocytes with slight atypia. Scattered multinucleated histiocytic giant cells are present which may show signs of elastophagocytosis and emperipolesis (phagocytosis of lymphoid cells). The bulky skin lesions usually involve the major skin folds and GSS occurs mostly in the third to fourth decades of life. The disease shows preponderance for indolent but persistent occurrence.

Sarcoidosis, tuberculosis and foreign body granulomas show more or less compact aggregates of epithelioid histiocytes and giant cell of Langerhans or other morphology, which presents tendency for a limited nodular arrangement with a lymphoid elements showing no signs of cellular atypia Subcutaneous panniculitis-like T-cell lymphoma involves the subcutis with pleomorphism of the lymphocytes and a peculiar tendency of atypical lymphocytes to create s.c. rimming of the lipocytes.

Additional literature:

Monika Bowszyc-Dmochowska MD PhD, Cases 7-13

Case 7
A 59 year-old woman with brown hyperkeratotic follicular papules on the left side of the trunk, forehead, temples and neck since adolescence, and painful erythematous lesions with erosions and small blisters under her left breast for few days. The diagnosis is:

C. Darier’s disease with herpes zoster infection (correct)
A. Hailey-Hailey disease (incorrect)
Because within an acanthotic epidermis there is only focal suprabasal acantholysis and dyskeratosis but no extensive epidermal acantholysis with the “dilapidated brick wall” appearance. There are something else in the upper part of the epidermis: keratinocytes with steel-grey nuclei and syncytial cells that aren’t typical for Hailey-Hailey disease (HHD). The clinical description “brown hyperkeratotic papules” doesn’t fit either.
B. Grover’s disease (incorrect)
Because beside the acantholytic clefts and focal dyskeratosis the clinical data are inconsistent with Grover’s disease. Transient acantholytic dermatosis is an itchy exanthem mainly in elderly males. Moreover there are nuclear changes typical for herpes infection in the epidermis.
C. Darier’s disease with herpes zoster infection (correct)
Because there is focally acanthotic epidermis with suprabasal acantholytic clefts and dyskeratosis (grains and corps ronds) and there are syncytial cells with 2-4 moulding nuclei with steel-grey central and peripheral condensation of chromatin typical for herpes simplex or zoster infection, in the epidermis.
D. Eczema herpeticum (incorrect)
Because suprabasal acantholysis and dyskeratosis are not typical for eczema or atopic dermatitis, and the clinical description is not typical for atopic dermatitis.
E. Pemphigus vulgaris (incorrect)
Because there is only focal acantholysis without real suprabasal blisters and dyskeratosis is not typical for pemphigus. Moreover, clinical symptoms like hyperkeratotic papules since adolescence do not fit with pemphigus vulgaris

Darier’s disease: Autosomal dominant genetic disease, 12q23-q24.1 (ATP2A2)
Clinical picture: Brown hyperkeratotic papules disseminate mostly in seborrheic areas of the body (forehead, neck, retro auricular areas, chest, back), sometimes with erosions and inflammation (mostly in intertriginous areas). Other features are hyperkeratotic palmar and solar pits, white papules on the oral mucosa and nail changes like dystrophia mediana canalisformis. The disease starts after puberty and lasts with some exacerbations till death. Segmental form of Darier’s disease also exists.
Histopathology: Focal acanthosis with suprabasal acantholysis (“row of tombstones” over elongated dermal papillae), keratin plugs with dyskeratotic grains and corps ronds in the upper stratum spinosum.

Herpes zoster infection
Clinical picture: Painful erythema with clusters of small blisters in linear and distribution along skin dermatomes. Typical localisation: one side of the trunk along ribs and upper, middle or lower side of the face.
Histopathology: Epidermis is edematous with ballooning degeneration of keratinocytes, with secondary acantholysis, intraepidermal or subepidermal blisters and necrosis. Infected keratinocytes are multinucleated (with nuclear molding) with steel grey nuclei with margined chromatid and intranuclear eosinophilic inclusions (Cowdry A bodies). Similar changes can be seen in hair follicles, sebaceous glands and eccrine ducts. Dense inflammatory infiltrate with activated CD30+ and CD56+ lymphocytes and vasculitis.

Case 8
A 57-year old woman with hyperkeratotic brown papule on inflammatory base in the upper abdominal region. Recurrent intertriginous inguinal and armpit lesions for twenty years, currently oligosymptomatic. Clinical diagnosis: Irritated seborrheic keratosis. The diagnosis is:

B. Hailey-Hailey disease superimposed on seborrheic keratosis

A. Warty dyskeratoma (incorrect)
Because warty dyskeratoma is sporadic, acquired, and unilesional form of Darier’s disease with acanthotic epidermis, suprabasal acantholysis and dyskeratotic grains and corps ronds at the base of follicular keratin plug. Whereas in this case, there is extensive acantholysis involving full thickness of the epidermis.
B. Hailey-Hailey disease superimposed on seborrheic keratosis (correct)
Because this acanthotic epidermal papule is composed, like seborrheic keratosis, of two populations of cells: small uniform suprabasal cells and those resembling normal spinous layer. Extensive acantholysis with “dilapidated brick wall” appearance is typical for Hailey-Hailey disease from which the patient is suffering for years. HHD usually manifests in skin folds like armpits (patient had small HHD lesion in the left armpit), inguinal region or breast folds, and folded epidermis around larger. Seborrheic keratosis can behave like them as well. The single sporadic lesion with features of HHD without inherited genetic defect is called acantholytic dyskeratotic acanthoma.
C. Squamous cell carcinoma – dyskeratotic (adenoid) (incorrect)
Because there is no cellular atypia and invasion
D. Melanoma in situ (incorrect)
Because there is no proliferation of atypical melanocytes
E. Inverted follicular keratosis (incorrect)
Inverted follicular keratosis (some call it irritated type of seborrheic keratosis) should have squamous eddies instead of massive acantholysis.

Spectrum of acantholytic / dyskeratotic disorders
Hailey-Hailey Disease
Acantholytic dermatosis of the genito-crural region
Acantholytic acanthoma
Grover’s disease (transient acantholytic dermatosis, with five patterns: Hailey – Hailey-like, Darier-like, pemphigus vulgaris-like, pemphigus foliaceus-like and spongiotic)
Darier disease
Segmental Darier
Warty dyskeratoma
Focal Acantholytic Dyskeratoais (FAD)
Pemphigus vulgaris
Pemphigus foliaceus
IgA pemphigus (IEN/intraepidermal neutrophilic type and SPD/subcorneal pustular dermatosis type)
Subcorneal pustular dermatosis (Sneddon-Wilkinson)
Impetigo contagiosa
Acantholytic actinic keratosis
Dyskeratotic (acantholytic, adenoid) SCC
Case 9
A 58 year-old woman with numerous purpuric plaques and nodules, 0.5-1.5 cm in diameter, some with erosions localized on buttocks, tights, elbows for few months. The diagnosis is:

B. Erythema elevatum diutinum

A. Leukocytoclastic vasculitis (incorrect)
Because the vasculitis here is too extensive for leukocytoclastic vasculitis (LCV) and the clinical picture like persistent nodular lesions on the upper part of the lower extremities and buttocks is not typical for LCV. The lesions in LCV are more numerous and more necrotic in more severe cases with predilection for the lower parts of the legs.

B. Erythema elevatum diutinum (correct)
Because there is an extensive vasculitis with fibrin deposits and neutrophils within destroyed blood vessel walls and massive neutrophilic infiltrate with leukocytoclasia and extravasated erythrocytes in the entire dermis. Despite of such intensive vasculitis there are no necrosis in the epidermis and dermis. The persistent purpuric nodules localised on the extensor areas of the elbows, knees, tights and buttocks are more consistent with EED than any other form of vasculitis.

C. Kaposi sarcoma (incorrect)
Because neutrophils are absent in KS and there are no spindle cells around blood vessels

D. Sweet syndrome (incorrect)
Because in Sweet syndrome there is massive neutrophilic infiltrate (perivascular and interstitial) and marked papillary dermal edema, but no vasculitis and red blood cell extravasation. The course of the disease is different with periodic recurrences preceded by fever and leucocytosis.

E. Pyoderma gangrenosum (incorrect)
Because the features typical for PG such as painful ulcer with hyperplastic epidermis and neutrophilic microabscesses are absent in this case.

Erythema elevatum diutinum

Clinical picture: Persistent dark red, violaceous, yellowish papules, plaques, nodules. Rarely pedunculated, bullous or verrucous lesions. Fibrotic nodules characterize lesions of long duration. Symmetric distribution on extensor surfaces of knees, elbows, buttocks, feet and other parts of extremities. Disease can last 5-20 years and is resistant to therapy including Dapsone, Corticosteroids, CyA, Chloroquine, and Tetracycline.

Sometimes associated with arthralgia, ulcerative keratitis, scleritis, pulmonary infiltrates, myelodysplastic syndrome, lymphoma, breast cancer, multiple myeloma, IgA monoclonal gammopathy, hypergammaglobulinemia D syndrome, antiphospholipid antibodies, cryoglobulinemia, inflammatory bowel diseases, and various autoimmune diseases. The MPO ANCA (pANCA ) and interstitial pulmonary fibrosis was reported in association with EED in one case. The etiology is unknown, probable Arthus-type reaction to bacterial or viral antigens.

Histopathology: In early and fully developed stages there is extensive leukocytoclastic vasculitis the dermis with extensive neutrophilic infiltrate in the entire dermis. The epidermis is uninvolved or with spongiosis rather than necrotic changes. In late lesions the capillary proliferation, concentric perivascular fibrosis (EED belongs to the so called localized chronic fibrosing vasculitis group) and sometimes granulomatous nodules or cholesterol deposits are present.

**Case 10**
A 57-year old man with hard nodules on elbows and buttocks, < 0.5 cm in diameter, for four years. Rheumatoid arthritis. The diagnosis is:

**D. Palisaded neutrophilic granulomatous disease**

A. Calcinosis cutis (incorrect)
Despite basophilic character of the granulomas there are no typical calcium deposits and no foreign body giant cells dominating in the infiltrate.

B. Rheumatoid nodule (incorrect)
Because rheumatoid nodule does not contain neutrophils and the central necrobiosis tend to be more eosinophilic (fibrinoid) than basophilic.

C. Sporotrichosis (incorrect)
Because in sporotrichosis the suppurative granulomas contain neutrophils in the central necrotic part of the granuloma. The Periodic acid Schiff (PAS)-positive sporotrichoid asteroids can be found in the suppurative granulomas or in the giant cells. The symmetrical and disseminated distribution is not typical for sporotrichosis.

D. Palisaded neutrophilic granulomatous disease (correct)
Because there is granuloma arranged in palisading pattern around necrobiotic basophilic collagen, composed of histiocytes, lymphocytes and numerous neutrophils. Granuloma is situated in the deep part of the dermis. Patient has rheumatoid arthritis (RA) and such neutrophilic granulomas are associated with RA as well as other CTD. Lesions are symmetrical and sometimes in linear distribution.

E. Sweet syndrome (incorrect)
Because of the granulomas have necrobiosis of the collagen and because the neutrophils are not the only cells in the infiltrate.

*Palisaded neutrophilic and granulomatous dermatitis and interstitial granulomatous dermatitis with arthritis* are the two variants of the granulomatous diseases associated with autoimmune diseases like rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome, autoimmune spondylitis, autoimmune hepatitis, diabetes mellitus, vasculitis and sometimes also with neoplasms such as lymphomas, leukemias, and metastatic carcinomas or various infectious diseases viral, bacterial or fungal.

**Clinical presentation:** Skin-colored cords on lateral part of the trunk ("rope sign") are typical for interstitial granulomatous dermatitis. Pink papules with umbilication or crusts and plaques symmetrically distributed mostly on elbows or fingers are typical for palisaded neutrophilic and granulomatous dermatitis.

**Histopathology:** Interstitial granulomatous dermatitis with arthritis resembles incomplete granuloma annulare with interstitial histiocytes, lymphocytes and neutrophils, and sometimes with occasional eosinophils.

Palisaded neutrophilic and granulomatous dermatitis is a type of granuloma with foci of degenerated basophilic collagen surrounded with neutrophils and palisade of histiocytes, giant cells and lymphocytes. The granulomatous infiltrate can occupy the entire dermis with accentuation of the process in the lower dermis.

Case 11
A 50-year-old woman with flat brown-yellow nodules and plaques on the trunk and multiple xanthelasmas on the face. Clinical diagnosis: Sarcoidosis. The diagnosis is:

E. Necrobiotic xanthogranuloma

A. Sarcoidosis (incorrect)
Because typical for sarcoidosis “naked” well-circumscribed epithelioid granulomas are absent in the biopsy material and necrobiosis with Tuton and xanthoma cells exclude sarcoidosis as well.

B. Atypical facial necrobiosis lipoidica (incorrect)
Because xanthoma cells and Tuton giant cells are absent in necrobiosis lipoidica even in atypical facial form.

C. Langerhans cell histiocytosis adult type (incorrect)
Because the Langerhans cells are epidermotropic so the infiltrate is usually dense in upper part of the skin and have characteristic kidney –shaped nuclei and the lesions are frequently localized in skin folds.

D. Xanthoma disseminatum (incorrect)
Because in XD there are numerous foamy histiocytes and Tuton giant cells but without necrobiosis and cholesterol clefts.

E. Necrobiotic xanthogranuloma (correct)
Because in the deep dermis there are foci of necrobiotic hyalinized collagen with cholesterol clefts surrounded by granulomatous infiltrate composed of histiocytes and giant cells with numerous Tuton cells and xanthoma cells.

Necrobiotic Xanthogranuloma

Clinical picture: NXG is multisystem, progressive disease, regarded as paraneoplastic. Patients usually have hepatosplenomegaly, arthritis, cardiomyopathy, pulmonary involvement, neuropathy, exophthalmos and haematological disorders. Paraproteinemia was present in almost all reported cases. Skin lesions are slowly enlarging papules, nodules and plaques, brown-red with yellow hue, rarely ulcerated. The lesions are located on the trunk or extremities with subsequent involvement of periorbital region where they have xanthelasma appearance. The mean time between the initial skin symptoms and the development of the haematological disease was 2.4 years. Patients with NXG require long-term follow-up for surveillance of monoclonal gammopathy or other hematologic diseases.

Histopathology: Granulomatous infiltrate occupies dermis and subcutis with extensive hyaline necrobiosis of collagen, cholesterol clefts that are surrounded by histiocytes, lymphocytes, xanthoma cells, and giant cells both foreign body and Tuton type. The cellular component is CD68+, and S100-, CD1a-.

Differential diagnosis: xanthoma, necrobiosis lipoidica, granuloma annulare, foreign body granuloma, rheumatoid nodule, Erdham-Chester disease.


Case 12
A 12 year-old boy with a rapidly growing 4 cm nodule with small blisters at the periphery and central necrotic crust on the left side of the chin. High fever and enlarged left submandibular lymph node. Patient had contact with a cat. The diagnosis is:

A. Cowpox

A. Cowpox (correct)
Because there is massive oedema, reticular degeneration and necrosis of the epidermis. Hair follicles show necrotic acantholysis of the external root sheath. In the remnants of hair follicle cells contain large intracytoplasmic eosinophilic inclusion bodies (type-A or Downie bodies) that push the nucleus to the periphery. There is also massive mixed inflammatory infiltrate. Patient had contact with cat, and cats are one of the most common sources of transmission of cowpox virus to humans. The polymerase chain reaction (PCR) test confirmed the presence of an Orthopoxviridae-specific genome fragment plus two cowpox-specific B9R and D11L fragments.

B. Cat scratch disease (incorrect)
Because in cat-scratch disease there should be the zone of necrosis surrounded by granulomatous infiltrate in the dermis and similar changes are seen in lymph nodes.

C. Herpes simplex (incorrect)
Because despite necrotic changes in the epidermis that goes down to the hair follicles the inclusion bodies (Cowdry A bodies) in herpes virus infection are intranuclear and there are steel-grey nuclei with peripheral accumulation of chromatin as well as multinucleated, syncytial cells. The size of the lesion and general symptoms were not typical for herpes simplex virus infection.

D. Primary cutaneous anaplastic large cell lymphoma (incorrect)
Because the epidermal and hair follicle necrosis are too extensive for PC ALCL. The infiltrate is too polymorphous. The presence of the inclusion bodies and immunohistochemistry performed on the serial sections exclude ALCL. The general symptoms like high fever do not fit either.

E. Leishmaniasis (incorrect)
Because in Leishmaniasis there should be massive dermal lympho-histiocytic infiltrate with parasitized macrophages containing leishmanial amastigotes – basophilic round to oval 2-4 µm structures in the early lesions and tuberculoid granulomatous infiltrate in late stages.

**Cowpox**
Cowpox is an uncommon zoonotic skin disease spreading mostly in Western Eurasia. The wild rodents are the natural reservoir of infection and domestic cats that become infected through hunting are one of the most common sources of transmission to humans. The condition is caused by a double-stranded DNA cowpox virus (CPXV), a member of the Orthopoxviridae genus that penetrates through wounded skin. At the site of infection one can observe an intensive immune reaction that may develop into necrosis. These symptoms are accompanied by fever and lymph node swelling. The disease is usually self-limiting. The diagnosis is confirmed by a polymerase chain reaction directed towards an Orthopoxviridae specific genome fragment.

**Histopathology**
The histopathological examination of skin biopsies in cowpox infection reveal eosinophilic cytoplasmic inclusion bodies in keratinocytes. During an infection of any of the Orthopoxviridae genus members, such as smallpox virus (variola), vaccinia virus, cowpox virus or monkeypox virus, these inclusions, known as Guarnieri bodies or type-B inclusion bodies are relatively small, eosinophilic, surrounded by a light halo and located in the cytoplasm of keratinocytes closely to the nucleus. These inclusions represent in fact the foci of viral replication. During the cowpox virus infection; however, there is an additional type of inclusion bodies, which are larger, similarly eosinophilic, yet may take a large portion of the cytoplasm and push the entire nucleus itself towards the perimeter of the cell. These are the so called type-A inclusion bodies, also known as Downie bodies. These usually contain mature virions. Such phenomena may also be found within the appendages of the skin, sweat and sebaceous glands and especially in fair follicles, where oedema or necrotic acantholysis of outer root sheath is seen. The presence of type-A or type-B inclusion bodies there may be a significant diagnostic indication when massive epidermal necrosis occurs. The infected epidermis is surrounded by a thick, mostly lymphocytic inflammatory infiltration, with additional histiocytes, eosinophils and CD30+ cells, which in general may arouse a suspicion of a lymphoma. However, the presence of a diverse population of lymphocytes allows differentiation
between the reactive and neoplastic character of such infiltration. The infiltration itself may cover an area from the epidermis and papillary dermis all the way down to subcutaneous tissue.

Case 13
A 40 year-old woman with 6 brown-grey plaques, 0.5-2.0 cm in diameter, on her face for more than 10 years. The diagnosis is:

E. Granuloma faciale

A. Primary cutaneous follicle center lymphoma (incorrect)
Because in PCFCL the infiltrate is composed of atypical lymphocytes not of neutrophils or eosinophils that dominate in this case
B. Persistent reaction to insect bite (incorrect)
Because the infiltrate (mixed with eosinophils) is usually wedge-shaped and it does not persist for years. The clinical picture: brown-grey persistent plaques, is not typical for persistent insect bite reaction
C. Acne agminata (incorrect)
Because in acne agminata chronic, granulomatous inflammatory infiltrate is concentrated around hair follicles rather than around blood vessels. Clinical picture is of perifollicular red inflammatory papules not grey-brown plaques.
D. Sarcoidosis (incorrect)
Because vasculitis, neutrophils and eosinophils are absent in sarcoidosis and there is no naked, epithelioid granulomas in the presented case
E. Granuloma faciale (correct)
Because there is dense, perivascular inflammatory infiltrate in the dermis that is separated from epidermis and appendages by grenz zone. The infiltrate is composed of neutrophils, lymphocytes, histiocytes and eosinophils. The neutrophils concentrate around blood vessels and infiltrate vessel walls. The lymphocytes, histiocytes and eosinophils are present in the peripheral part of the infiltrate.

Granuloma faciale belongs to the group of chronic, localized, fibrotic vasculitis.
Clinical picture: One or several brown-red plaques, papules or nodules usually on the face. Lesions tend to be asymptomatic or slightly pruritic and persistent. The similar lesion in the larynx was published under the name of angiocentric eosinophilic fibrosis.
Histopathology: Dense dermal polymorphous inflammatory infiltrate that is separated from hair follicles and epidermis by narrow grenz zone. In the center of the infiltrate around blood vessels there is an accumulation of neutrophils and mild leukocytoclasia with features of leukocytoclastic vasculitis. At the periphery lymphocytes, histiocytes and eosinophils dominate. Plasma cells, extravasated erythrocytes and sometimes few foam cells or giant cells may be present. In old lesions there is concentric fibrosis around blood vessels.
Direct immunofluorescence studies: immunoglobulins particularly IgG and complement are often present along dermo-epidermal junction and around blood vessels in linear-granular pattern.
Mai Hoang MD, Cases 19-22

Case 19
A 2.5 month-old female presented with a rash that started on the forehead soon after birth, then spread to trunk and extremities over a couple of days. Multiple targetoid, erythematous patches, some with scale were seen. Her parents were with no significant medical history. The best diagnosis for this case is:

B. Neonatal lupus erythematosus

A. Erythema multiforme (incorrect). Normal stratum corneum and prominent superficial dermal inflammatory infiltrate would be seen in erythema multiforme.
B. Neonatal lupus erythematosus (correct). The histologic findings of an interface dermatitis with dermal mucin deposition together with the clinical history are supportive of neonatal lupus erythematosus. Although cholestatic hepatobiliary disease, mild hemolytic anemia, transient thrombocytopenia, and leukopenia are complications that can be seen in association with neonatal lupus erythematosus, congenital heart block is the most feared complication. These two autoantibodies are associated with both neonatal lupus erythematosus and subacute cutaneous lupus erythematosus.
C. Subcutaneous lupus erythematosus (incorrect). Although the histology of subacute cutaneous lupus erythematosus and neonatal lupus erythematosus are similar, the clinical presentation of this case would not fit for subacute cutaneous lupus erythematosus.
D. Discoid lupus erythematosus (incorrect). Prominent hyperkeratosis, follicular plugging and marked dermal inflammatory infiltrate would be seen in discoid lupus erythematosus.
E. Drug hypersensitivity reaction (incorrect). Although interface dermatitis would be seen in a drug hypersensitivity reaction, dermal eosinophils rather than mucin deposition would be seen in the dermis.

Neonatal lupus erythematosus is an uncommon disease in which newborns have circulating anti-Ro/SSA and/or anti-La/SSB, but rarely anti-U1RNP, autoantibodies that are acquired transplacentally from the mother. The incidence is approximately 1:20,000 live births. About 50% of symptomatic neonates will present with cutaneous symptoms, with the remainder having cardiac disease; some 10% have both. Clinically, annular and scaly plaques affecting the face, scalp, then trunk and extremities are seen within days to weeks of birth with a predilection for sun-exposed areas. The most feared complication is congenital heart block which can result in mortality as high as 20-30% with most deaths occurring within the first 3 months of life. Neonatal lupus erythematosus accounts for 85% of congenital heart block cases with two-third of cases requiring pacemakers. While the cutaneous lesions often resolve by the age of 6 months, the congenital heart block is permanent. Other clinical complications include cholestatic hepatobiliary disease, mild hemolytic anemia, transient thrombocytopenia, and leukopenia. The mothers may have systemic lupus erythematosus or other autoimmune diseases. Those affected by neonatal lupus erythematosus have an increased risk of developing autoimmune diseases later in life.

Neonatal lupus erythematosus is associated with anti-Ro (SS-A) and/or anti-La (SS-B) autoantibodies which are also seen in subacute cutaneous lupus erythematosus. Histopathologically, neonatal lupus erythematosus has similar features to subacute cutaneous lupus erythematosus. They are vacuolar interface dermatitis, scattered epidermal apoptotic keratinocytes, sparse dermal inflammatory infiltrate, and dermal mucin deposition. In contrast to discoid lupus erythematosus, hyperkeratosis, follicular plugging, basement membrane thickening, pigment incontinence, and adnexal involvement are not prominent in neonatal lupus erythematosus. However, epidermal atrophy, interface changes and dermal mucin deposition may be more pronounced. The main histologic differential
diagnosis is erythema multiforme in which the marked dermal inflammatory infiltrate, apoptotic keratinocytes, and absence of direct immunofluorescence findings would be seen. Although the mechanisms responsible for neonatal lupus erythematosus have not been fully characterized, there is strong evidence to support the hypothesis that maternal anti-Ro/SSA and anti-La/SSB autoantibodies are involved in the pathogenesis. How and why maternal autoantibodies affect the target organs in such variable ways is unclear, although it is apparent that the fetal heart is uniquely vulnerable. Although uncommon, neonatal lupus erythematosus has important implications for both mother and child, and early recognition is essential.


**Case 20**
50-year-old man with no major past medical history presented with a fever of 102.2 and a diffuse erythematous eruption. The best diagnosis for this case is:

E. Acute generalized exanthematous pustulosis

A. Pustular psoriasis (incorrect)
B. Pustular contact dermatitis (incorrect)
C. Bullous leukocytoclastic vasculitis (incorrect)
D. Subcorneal pustular dermatosis (incorrect)
E. Acute generalized exanthematous pustulosis (correct). Subcorneal and intraepidermal pustules would be identified. In addition, marked papillary dermal edema and occasional dermal eosinophils would be seen.

In a 1968 series of 104 cases of generalized pustular psoriasis, Baker and Ryan reported 5 cases that occurred in patients with no history of psoriasis and raised the possibility of either infection or drug in the etiology. In 1980, Beylot et al introduced the term acute generalized exanthematous pustulosis (AGEP) in the French literature to describe pustular eruptions with the following characteristics: (1) an acute onset in patients with no history of psoriasis after infection and/or drug ingestion less than one day, (2) spontaneous resolution in less than 15 days, and (3) histologically non-follicular subcorneal pustules.

**Clinical presentation:** The typical cutaneous eruption of AGEP most commonly began either on the face or intertriginous areas and disseminated within few hours of ingestion of the offending agent. Non-follicular and less than 5mm pustules arose on edematous and erythematous skin with associated pruritis and/or burning sensation. Most patients had more than 100 pustules. The mean duration of the pustules was 9.7 days (range, 4 to 30 days). Desquamation followed in a few days. It appears that greater than 90% of AGEP cases are drug induced.

**Histopathology:** In the series of 63 cases by Roujeau et al, the main histologic findings of AGEP were spongiiform superficial pustules, papillary dermal edema, polymorphous perivascular infiltrate with eosinophils, and leukocytoclastic vasculitis with fibrinoid necrosis. In most cases the epidermis was uninvolved or exhibited spongiosis without psoriasiform hyperplasia. Focal necrosis of keratinocytes was noted.
Differential diagnosis of AGEP in adults includes pustular psoriasis, subcorneal pustular dermatosis, pustular contact dermatitis, bullous leukocytoclastic vasculitis, and drug hypersensitivity syndrome. Both AGEP and pustular psoriasis have intraepidermal or subcorneal spongiform pustules. However, marked papillary dermal edema, presence of eosinophils, and necrotic keratinocytes are more supportive of AGEP. Pustular eruption of Sneddon-Wilkinson/ subcorneal pustular dermatosis exhibits only subcorneal pustules (Figures 9 and 10); whereas intraepidermal pustules are noted in AGEP. A few cases of pustular contact dermatitis have been reported in the literature.

Bullous lesions may arise in lesions of leukocytoclastic vasculitis. Small-vessel vasculitis would be the predominant histology. Confusion may occur due to the occasional presence of vasculitis in AGEP. Drug hypersensitivity syndrome, or DRESS (drug rash with eosinophilia and systemic syndrome), might have pustules but usually less pronounced than that seen in AGEP. In addition, the patients also have fever, lymphadenopathy, eosinophilia, mononucleosis, and often severe visceral involvement like hepatitis, nephritis, pneumonitis, and/or myocarditis.


Case 21
22 month-old girl with four-day history of perioral impetigo with progression to superficial skin desquamation and erythema involving 30% of body surface area. Hemorrhagic crust was seen around eyes and nose. The best diagnosis for this case is:

D. Staphylococcal scalded skin syndrome

A. Bullous impetigo (incorrect). Bacteria would be seen on Gram stain in bullous impetigo.

B. Dermatophytosis (incorrect). PAS stain would demonstrate fungal elements within the stratum corneum.

C. Pemphigus foliaceus (incorrect). Although separation is noted at the granular layer, direct immunofluorescence would demonstrate intercellular IgG and C3 deposition within the epidermis.

D. Staphylococcal scalded skin syndrome (correct)

Staphylococcal scalded skin syndrome (SSSS) is caused by exfoliative (or epidermolytic) toxin produced by coagulase-positive group II Staphylococcus aureus (especially strain 71). Currently, the role of exfoliative toxins in the pathogenesis of SSSS is not well defined. SSSS often starts as skin tenderness, erythema in flexural skin and with mucous membrane sparing. Subsequently large flaccid blisters with positive Nikolsky sign develop which rupture readily. Widespread exfoliation which can involve most of the body surface (Ritter’s disease) is caused by toxin produced from infection at distant site and reach the cutaneous target via hematogenous spread. Significant skin sloughing can result in poor thermoregulation, delicate fluid balance and susceptibility to superinfection. SSSS mainly affects neonates and children less than 6 years of age likely due to an immature immune system and less effective renal toxin clearance.

E. IgA pemphigus (incorrect). Direct immunofluorescence examination would show intercellular IgA deposition within the epidermis.
Case 22
83 year-old man w/ painful blistering eruption over scrotum → trunk → acral skin x 2 weeks. The best diagnosis for this case is:

**B. Anti-p200 (anti-laminin gamma-1) pemphigoid**

A. Bullous pemphigoid (incorrect)
B. Anti-p200 (anti-laminin gamma-1) pemphigoid (correct)
C. Linear IgA disease (incorrect)
D. Dermatitis herpetiformis (incorrect)
E. Bullous drug eruption (incorrect)

**Anti-p200 pemphigoid** is an uncommon, acquired, subepidermal bullous disease. Recent evidence suggests that laminin γ1, a non-collagenous N-linked glycoprotein that facilitates adhesion in the lower lamina lucida of the dermal-epidermal junction, is the putative target for autoreactive antibodies in these patients.

**Clinical presentation** most often demonstrates pruritic papules and urticarial plaques admixed with tense bullae, predominantly on the trunk and extremities.

**Histopathology:** The histopathologic features are characterized by subepidermal bullae and a neutrophilic inflammatory infiltrate with periodic microabscesses or eosinophils in the papillary dermis. While such findings can overlap with lesional skin in other bullous diseases, this pathologic picture combined with clinical presentation should prompt further workup, including immunofluorescence and immunoblotting studies for definitive diagnosis. The pemphigoid family of disorders normally demonstrate linear deposits of IgG and C3 along the dermal-epidermal junction on direct immunofluorescence examination. Indirect immunofluorescence studies using NaCl-treated split normal human skin as a substrate, circulating autoantibodies in patients with anti-p200 pemphigoid bind to the dermal side of the split skin whereas other pemphigoid family disorders such as bullous pemphigoid, linear IgA and pemphigoid gestations typically bind the epidermal side of split skin. While epidermolysis bullosa acquisita and some variants of mucous membrane pemphigoid also demonstrate dermal staining on indirect immunofluorescence, serological analysis via immunoblotting on human dermal extracts can definitively differentiate these conditions. In patients with anti-p200 pemphigoid immunoblotting can identify a 200-kDA protein, now known to be laminin γ1. Given that such serologic analysis is only available at specialized laboratories, a relatively sensitive and highly specific enzyme-linked immunosorbent assay (ELISA) for anti-p200 pemphigoid has recently been developed.