Self-Assessment Answers Cases 27 - 50

Chairs:

Sara Edward (UK)

Anjela Galan (USA)

Self-Assessment Answers

Part 3 – Saturday 30th September 2017

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Case 27
Madhavi Maheshwari

DIAGNOSIS:
EPITHELIOID SHWANNOMA

Clinical Summary:
27 female, mobile, non-fluctuant swelling dorsum of foot? Lipoma

Microscopic Features:
Sections show a nodular, well defined capsulated lesion made up of small round cells having high nuclear cytoplasmic ratio with prominent nucleoli in some of the cells. Few pseudo inclusions are seen. These cells are arranged in large nests and in places have a rosetting arrangement with central fibrillary/eosinophilic background including pseudo rosettes around blood vessels which are slightly thick walled. Mast cells are scattered throughout the lesion. Scattered mitotic figures are seen. No high grade changes or necrosis is visible.
The cells are strongly immunoreactive for S100 and CD56, whilst being patchily positive for NSE and CD57. They are negative for HMB45, Melan A, SMA, Desmin, PGP9.5, Chromogranin, Synaptophysin, CD99, CD31 and CD34. EMA is seen surrounding the lesion suggestive of perineurium.

Discussion:
The differentials here are a neural or a melanocytic lesion. The presence of mast cells, rosettes, fibrillary background with perineurial sheath on the outside all favours a neural lesion. The morphology and immunohistochemistry is of an Epithelioid schwannoma. The presence of small epithelioid cells like glomus cells has also been called neuroblastoma like schwannoma. The differential diagnosis includes Epithelioid malignant peripheral nerve sheath tumour which is unlikely as the lesion is superficial, mobile with no necrosis or marked cytological atypia. Neuroendocrine markers being positive raises the possibility of PNET but CD99 is negative and the morphology is bland. Melanoma is unlikely as Melan A and HMB45 are negative and the cells are monotonous.
Epithelioid Schwannoma is a benign nerve sheath tumour and is based in the dermis or subcutaneous tissue. Histologically all cases have an epithelioid morphology and the cellularity varies depending on the proportion of cells and stroma which can be hyaline or myxoid. It is more likely to be mistaken for epithelioid malignant peripheral nerve sheath tumour. Other possible differential diagnoses include glomus tumour, malignant melanoma, soft tissue myoepithelioma and epithelioid neurothekeoma. Atypical variants have been described as showing diffuse or marked nuclear atypia and mitosis >3/10HPF. Benign as well as atypical variants have not shown any evidence of recurrence even if incompletely excised. Most of the cases are sporadic but occasionally have been associated with schwannomatosis.

References:
1. Epithelioid Schwannomas: An Analysis of 58 Cases Including Atypical Variants. Hart J, Gardner JM, Edgar M, Weiss SW. Am J Surg Pathol. 2016 May; 40(5):704-13

Case 28

Máirín McMenamin

DIAGNOSIS: PALISADED NEUTROPHILIC AND GRANULOMATOUS DERMATITIS IN THE SETTING OF DOUBLE-SEROPOSITIVE PERINUCLEAR ANTINUCLEAR CYTOPLASMIC ANTIBODIES (ANTI-MYELOPEROXIDASE) AND ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODIES. A CLINICAL DIAGNOSIS OF DOUBLE-SEROPOSITIVE MICROSCOPIC POLYANGIITIS WAS MADE.

Clinical Summary:
67 year old male with a history of ischemic heart disease, hypertension, aortic aneurysm, type 2 diabetes mellitus and gout, on multiple medications (including allopurinol), presented with new onset renal impairment. He was diagnosed with microscopic polyangiitis with double-seropositive perinuclear anti-neutrophil cytoplasmic antibody (anti-myeloperoxidase, anti-MPO) and anti-glomerular basement membrane (anti-GBM). He reported a 6 month history of arthralgia, tender skin ulcers and some flesh- colored papulonodules, located mainly on extensor surfaces and buttocks. Clinical differential diagnoses included vasculitis, infection, lymphomatoid papulosis and xanthomas. A 4mm punch biopsy was taken of a papule on his left elbow.

Microscopic Features:
Sections show florid dermal palisaded neutrophilic and granulomatous dermatitis comprising basophilic or 'blue' granulomas caused by neutrophil infiltrates with leukocytoclasis, associated with degeneration of collagen and surrounded by epithelioid macrophages. Focal skin ulcer is present and no vasculitis is identified. Stains for microorganism (Gram, PAS and ZN) are negative.

Discussion:
Palisaded neutrophilic and granulomatous dermatitis (PNGD) is a classic but uncommon condition that mainly affects adults and is associated with connective tissue diseases, especially rheumatoid arthritis, systemic lupus erythematosus, granulomatosis with polyangiitis (formerly Wegener's granulomatosis) and granulomatosis with polyangiitis and eosinophilia (formerly Churg-Strauss syndrome). Cases have also been reported in association with adult onset Still's disease, ankylosing spondylitis, systemic sclerosis, Behçet's disease, ulcerative colitis, sarcoidosis, chronic myelomonocytic leukemia and drugs (allopurinol and tumour necrosis factor-alpha inhibitors). There is a report of associated hypercalcemia and transient liver dysfunction. Some cases have had no associated conditions. The typical clinical presentation is of umbilicated or ulcerated flesh-colored papulonodules on extensor surfaces. Lesions can be asymptomatic or tender. This patient was considered to have microscopic polyangiitis with dual positive anti-MPO and anti-GBM. Due to the risk of stopping aspirin in severe ischemic heart disease, renal biopsy was not performed. He was treated with a steroid sparing regimen that included rituximab and cyclophosphamide and subsequently with dapsone. Allopurinol

was stopped temporarily. He showed resolution of skin lesions and an improvement in renal function.

Treatment of PNGD includes treatment of the underlying systemic condition. Some cases are self-limited. Topical or intralesional triamcinolone, oral steroids, dapsone, colchicine, mycophenylate mofetil, cyclosporine, cyclophosphamide, hydroxychloroquine and non steroidal anti-inflammatory agents have been used with variable success. Recurrence has been reported on treatment withdrawal. Some authors consider PNGD to be part of the spectrum of neutrophilic dermatoses, as the earliest lesions are neutrophilic and coexistent leukocytoclastic vasculitis has been reported in some patients. Other authors consider that PNGD forms part of a spectrum of reactive granulomatous dermatitis that includes interstitial granulomatous dermatitis and interstitial granulomatous drug reaction. It has been reported that dual seropositivity for pANCA (anti-MPO) and anti-GBM suggests a less acute course than anti-GBM disease, better renal survival but no difference in overall survival compared to anti-GBM disease. Weakly positive pANCA (anti-MPO) can also be seen in a variety of infective and inflammatory conditions, including aortic aneurysm. Careful clinical correlation is required in PNGD, including thorough medical and medication history, systems review and appropriate laboratory investigations.

References:

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2. Sangueza OP, et al. Palisaded neutrophilic granulomatous dermatitis in rheumatoid arthritis. J Am Acad Dermatol 2002; 27:251-7.

3. Hau E, et al. Neutrophilic skin lesions in autoimmune connective tissue diseases. Medicine 2014;93:e346.

4. Rosenbach M, English JC. Reactive granulomatous dermatitis: a review of palisaded neutrophilic and granulomatous dermatitis, interstitial granulomatous dermatitis, interstitial granulomatous drug reaction, and a proposed reclassification. Dermatol Clin. 2015; 33: 373-87.

5. McAdoo SP, et al. Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse and outcomes compared to single-seropositive patients. Kidney Int 2017;pii:S0085-2538(17)30207-7. doi:10.1016

Case 29
Dr William Merchant

DIAGNOSIS:
POROKERATOSIS PTYCHOTROPICA

Clinical Summary:
45 Male, Gluteal biopsy. 10 year history of progressive itchy flat topped papules and warty plaques on both buttocks.

Microscopic Features:
Irregular epidermal acanthosis and papillomatosis associated with hyperkeratosis giving a verrucous appearance. There are several columns of parakeratin associated with loss of the granular layer present . These are associated with dyskeratosis beneath these parakeratotic columns. These changes are indicative of cornoid lamellae which is the hallmark feature of Porokeratosis.

Discussion:
Porokeratosis consists of a group of disorders of keratinization in which cornoid lamellae is the defining feature. Each variant has a different clinical presentation. Porokeratosis ptychotropica was first described in 1995 [1] and has distinct clinical features. It presents with symmetrical, verrucous plaques on both buttocks and anal cleft giving a 'butterfly' appearance. A peripheral ridge maybe identified which corresponds to the cornoid lamella. Porokeratosis ptychotropica comes from the Greek words ptyche (fold) and trope (a turning) to indicate is predilection for the natal cleft. Males appear to be much more commonly affected. It is often itchy, which is unusual for porokeratosis, and there is usually a long history of many years with gradual extension of the lesion. It is not associated with any other conditions or disease elsewhere in the body. Treatment appears difficult as it does not respond to conventional treatment but some recent articles have reported success with imiquinod [3] and photodynamic therapy [4]
Porokeratosis in general has been associated with an increased risk of malignancy. The risk in this variant is unclear but there has been one recent report of a Squamous Carcinoma arising with it (5).

References:
1. An unusual case of porokeratosis involving the natal cleft: porokeratosis ptychotropica? Br J Dermatol. 1995 Jan;132(1):150-1. Lucker GPH, Happle R, Steijlen PM.

2. Porokeratosis ptychotropica: a rare and evolving variant of porokeratosis. Yeo J, Winhoven S, Tallon . B. J Cutan Pathol 2013: 40: 1042–1047

3. Porokeratosis ptychotropica responding to photodynamic therapy: An alternative treatment for a refractory disease. Fustà-Novell X, Podlipnik S, Combalia A, Morgado-Carrasco D, Ferrando J, Mascaró JM Jr, Aguilera P.
Photodermatol Photoimmunol Photomed. 2017 Jun 5. doi: 10.1111/phpp.12319. [Epub ahead of print]

4. A case of porokeratosis ptychotropica: successful treatment with topical 5% imiquimod cream. Kawakami Y, Mitsui S. Clin Exp Dermatol. 2017 May 22. doi: 10.1111/ced.13117. [Epub ahead of print]

5 Transformation of porokeratosis ptychotropica into invasive squamous cell carcinoma. Mazori DR, Shvartsbeyn M, Meehan SA, Tarsis SL.
Int J Dermatol. 2017 Jun;56(6):679-680. doi: 10.1111/ijd.13575. Epub 2017 Feb 15. PMID: 28197991 [PubMed - in process]

Case 30
Cosimo Misciali

DIAGNOSIS: ONYCHOMATRICOMA

Clinical Summary:
A 69 years old women presented an asympomatic thickening of the nail plate of the second finger of right hand for three years. At clinical examination thickened and yellowish nail plate was observed with longitudinal grooves and transversal hypercurvature.

Microscopic Features:
OM is a tumor of the nail matrix composed by multiple distal fibroepithelial projections and a thick keratogenous zone forming multiple V-shaped invaginations at the level of epithelial ridges, with the formation of a thick nail plate. The epithelium that covers the projections has no granular layer.

Discussion:
Onychomatricoma is a rare benign fibroepithelial tumor of nail matrix that occurs in the digits of both the hands and feet, first described by Baran and Kint in 1992. The clinical index of suspicion for onychomatricoma should increase when only a singular dystrophic nail is involved. Following diagnostic confirmation by histopathology, complete surgical excision is the treatment of choice.

References:
1. Baran R, Kint A. Onychomatrixoma. Filamentous tufted tumour in the matrix of a funnel-shaped nail: a new entity (report of three cases). *Br J Dermatol*. 1992 May. 126(5):510-5.

2. Perrin C, Baran R, Pisani A, et al. The onychomatricoma: additional histologic criteria and immunohistochemical study. *Am J Dermatopathol*. 2002 Jun. 24(3):199-203.

Case 31
Dr Nitin Khirwadkar

DIAGNOSIS
METASTATIC NEUROENDOCRINE CARCINOMA TO THE SKIN

Clinical Summary:
Male 58 years with a nodule on the back

Microscopic Features:
The sections show fibrofatty tissue, without epithelium, containing a tumour with pushing and infiltrative margins. The tumour cells have moderate amounts of eosinophilic cytoplasm, and contain nuclei with mild and moderate cytonuclear atypia. Focal, mitoses are easily seen. The tumour cells form rosettes and pseudo-rosettes. The tumour is present within a sclerotic background. The tumour cells are positive for neuroendocrine markers PGP9.5, CD56, synaptophysin and chromogranin. The Ki67 proliferation rate ranges from 10-15%. There is weak, patchy, cytoplasmic expression for CK20. The tumour is negative for CK7, TTF-1 and PSA.

The appearances are those of a metastatic , WHO grade 2, well differentiated neuroendocrine carcinoma.

Discussion:
Well differentiated neuroendocrine tumours metastasize to the skin uncommonly, and only a few cases have been reported in the literature. Cutaneous metastasis may be the first sign of clinically silent visceral cancer (37% in men and 6% in women) or even a clue to tumor recurrence. Therefore, the detection of skin metastases requires a high index of clinical suspicion and the final diagnosis is established by histopathology.

The distinction from other microscopically similar entities, and the interpretation of the primary site of origin, is made from the clinical/imaging investigations and also on immunophenotypic features.

Carcinoid tumors are neuroendocrine tumors derived from enterochromaffin cells, which are widely distributed in the body. Carcinoid tumors from various anatomic locations may metastasize to skin, the bronchus being the most frequent site for primary carcinoids producing cutaneous metastases.
This case represents cutaneous metastasis of a well differentiated neuro-endocrine carcinoma of the small bowel (ileum). The patient had this resected in 2009 and presented with the cutaneous nodule in 2016.

References:
1. J Jaroslaw, K Busam, D Klimstra & M Pulitzer. Cutaneous metastases as an initial manifestation of visceral well-differentiated neuroendocrine tumor: a report of four cases and a review of literature. J Cutan Pathol. 2014;41(2):113-122.

2. I Alcaraz, L Cerroni, A Ru¨ tten, H Kutzner & L Requena. Cutaneous Metastases From Internal Malignancies: A Clinicopathologic and Immunohistochemical Review. Am J Dermatopathol. 2012; 34(4): 347-393.

Case 32
Dr Uma Nahar

DIAGNOSIS:
MYCOSIS FUNGOIDES BULLOSA

Clinical Summary:
A 48 year old male with Erythematous plaque with vesicobullous lesion all over body for 6 months

Microscopic Features:
Acanthotic epidermis with spongiosis and focal intraepidermal clefting forming blister. Infiltration by large atypical lymphoid cells with irregular and hyperchromatic nuclei within the entire dermis and infiltrating the epidermis as well.
In addition similar cells also seen within the cleft with focal epidermotropism and putriers microabscess formation. Folliculotropism is also noted.

Discussion:
Mycosis fungoides(MF) is the most common cutaneous T cell Lymphoma and bulla formation is very uncommon. Mycosis fungoides bullosa is extremely rare usually seen in older age group and only 20 cases have been reported in the literature. It is a clinical subtype of CTCL and has an aggressive clinical course with poor prognosis. Approximately 50% of patients die within 1 year of diagnosis. The mechanism of blister formation is not clearly elucidated whihc could be Confluence of Pautrier's microabscesses leading to intra-epidermal bulla formation. proliferation of neoplastic lymphocytes resulting in loss of coherence between basal keratinocytes and basal lamina or by the release of lymphokines by atypical lymphoid cells. However, other concomitant autoimmune bullous lesions needs to be excluded by immunofluorescence. In addition other causes of secondary vesiculobullous lesions asscociated with MF eg, bacterial or viral infection, medications, porphyria, phototherapy should be ruled out.

References:
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3. Kneitz H[1], Bröcker EB, Becker JC Mycosis fungoides bullosa: a case report and review of the literature. J Med Case Rep. 2010 Mar 3;4:78. doi: 10.1186/1752-1947-4-78.

Case 33

Nicolas Ortonne

DIAGNOSIS
DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) SIMULATING A CUTANEOUS T-CELL LYMPHOMA

Clinical Summary:
He presented with an erythroderma with fever, and edema of the limbs. Clinical examination revealed inguinal adenopathies. Blood cell count and smears analyses disclosed and hypereosinophilia with presence of hyperbasophilic lymphocytes. He had a slight increase of hepatic enzymes (<2N).

Microscopic Features:
Skin biopsy showed a dense lymphocytic infiltrate in the superficial and mid dermis, with basal epidermotropism. Focal interface dermatitis changes were seen, with vacuolated keratinocytes and few apoptotic cells. The infiltrate was composed of small to medium sized lymphocytes and comprised cells with slight nuclear atypia. No eosinophils and no neutrophils were seen.
Immunophenotypic studies revealed that the infiltrate was mainly composed of T lymphocytes without T-cell antigen loss (CD2+, CD3+, D5+, CD7+), made of a mixture of CD4+ and CD8+ cells. Numerous cytotoxic lymphocytes (granzyme B+) were identified. CD30 staining was negative as well as CD10 and CXCL13, while PD1 was weakly expressed. Only few CD20+ B-cells were seen.

Discussion:
The term "drug rash with eosinophilia and systemic symptoms (DRESS)" was introduced by Bocquet and colleagues in 1996, because the ancient denomination of “hypersensitivity syndrome” was considered ambiguous. In most patients, DRESS is characterized by a skin rash and multi-visceral involvement, usually associated with hypereosinophilia (1). DRESS can present with more aggressive cutaneous lesions, including an erythroderma or with bullae, with patients presenting overlapping features with toxic epidermal necrolysis (TEN). The delay between introduction of the culpit drug and onset of the disease varies between 10 to 40 days. The pathophysiology relies on a delayed hypersensitivity reaction with activation of drug specific T-cells. The role of anti-viral responses has been suspected because many patients have concomitantly a re-activation of EBV, CMV, HHV6 or 7 infections. The histopathological aspect of DRESS has better been described in the literature, with several retrospective case series published during the recent past years (2-4). All highlighted the polymorphous aspect of skin lesions, with various inflammatory patterns from one case to another and even in a single biopsy (4).
In cases with diffuse skin eruption or erythroderma and adenopathies, differential diagnosis with a lymphoma, especially Sézary syndrome (SS) or angio-immunoblastic T-cell lymphoma (AITL), may be difficult. The presence of a dense epidermotropic infiltrate made of cytotoxic CD8+ T-cells can also make the differential diagnosis with the rare primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma challenging. The possible confusion with a cutaneous T-cell lymphoma on histopathological grounds is in part due to the fact that the inflammatory infiltrates of DRESS may comprise atypical lymphocytes. They may be observed

in up to 20% of cases (4). In addition, it has been shown that T-cell clonality analyses may supply positive results in DRESS.
The differential diagnosis can be done upon clinical, biological and histopathological parameters, as summarized in Tables 1 and 2. The distinction between DRESS and a cutaneous lymphoma is important because the treatments are different. DRESS usually resolves under systemic steroids. Nevertheless, aggressive forms can be life-threatening, either because of eosinophilic myocarditis or colitis, severe haemophagocytic syndrome, fulminant hepatitis or extended skin detachment as in TEN.

Table 1. Clinical and biological features of DRESS and cutaneous lymphoma mimics

Diagnosis	**Erythroderma**	**Systemic symptoms**	**ADP**	**Atypical lymphocytes in blood**	**Hyper-eosinophilia**	**EBV reactivation**
Sézary	+	+	+	+ (Sézary cells)	-	-
AITL	Possible	+	+	Rare	+	+
PCAETCL	-	Possible	-	-	-	-
DRESS	Frequent	+	+	Frequent (hyperbasophilic)	+	+

Table 2. Pathological features of DRESS and cutaneous lymphoma mimics

Diagnosis	**Inflam ma-tory feature s***	**Epider mo-tropism**	**Atypical lymphoc ytes**	**T-cell Ag loss**	**Phenotype of atypical cells**	**EBV+ B-cells**	**Skin T-cell clone**
Sézary	Possible	Frequen t	Frequent	Possible (CD7>CD2)	CD4+, PD1+	-	+
AITL	Rare	Rare	Frequent	Possible	CD4+, CD10+/- CXCL13+, PD1+	Possib le	+
PCAETCL	Possible	+	+	Frequent	CD8+ perf/GrB+	-	+
DRESS	Frequen t	Frequen t	Possible	-	CD8>CD4 perf/GrB+	Rare	Rare

PCAETCL : primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma.
* Lichenoid or spongiotic reaction pattern

References:

1. Kardaun SH, Sekula P, Valeyrie-Allanore L et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013; 169: 1071-80.

2. Chiou CC, Yang LC, Hung SI et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. *J Eur Acad Dermatol Venereol* 2008; 22: 1044-9.

3. Chi MH, Hui RC, Yang CH et al. Histopathological analysis and clinical correlation of drug reaction with eosinophilia and systemic symptoms (DRESS). *Br J Dermatol* 2013; 170: 866-73.

4. Ortonne N, Bastuji-Garin S, Allanore L, et al. Histopathology of drug rash with eosinophilia and systemic symptoms (DRESS): a morphologic and phenotypic study. Br J Dermatol 2015;173(1):50-8

Case 34

Rajiv M. Patel, M.D.

DIAGNOSIS
PAPILLARY INTRAEPITHELIAL ANGIOENDOTHELIOMA (PILA)

Clinical Summary:
Two year old female presents with a left distal ring finger mass

Microscopic Features:
- Poorly demarcated dermal or subcutaneous proliferation of lymphatic channels
- Intraluminal papillations composed of hyaline cores lined by hobnail endothelial cells, which lack frank cytologic atypia
- Relatively little mitotic activity
- Intermixed intraluminal lymphocytes
- Immunoreactivity for vascular (CD31, CD34, ERG,VEGFR3) and lymphatic (D2-40, PROX-1) markers

Discussion:
Papillary intraepithelial angioendothelioma (PILA), also known as Dabska tumor and retiform hemangioendotheliomas (RHE) are closely related vascular tumors of intermediate malignancy, which have the capacity to locally recur and extend to local lymph nodes, but rarely metastasize to distant sites. Both tumors are characterized by hobnail endothelial cells leading to their collective alternative designation of hobnail hemangioendothelioma. PILA is characterized by well-formed vessels with intraluminal papillations composed of hyaline cores lined by hobnail endothelial cells, while the cardinal features of RHE consist of elongated vessels resembling the rete testis, which are lined by a single layer of hobnail endothelial cells. Hybrid lesions are occasionally encountered. PILA typically occurs in children, while RHE is seen more often in adults. Approximately half of PILA cases occur in the distal extremities, but other site may be affected. The lesions are positive for vascular (CD31, CD34, ERG, VEGFR3) and endothelial (D2-40, PROX-1) markers by immunohistochemistry. The lymphatic immunophenotype of PILA is confirmed by immunoreactivity for D2-40 (Podoplanin) and VEGFR3. The differential includes predominantly other benign (epithelioid hemangioma, juvenile hemangioma, pyogenic granuloma, lymphangioma) and malignant (angiosarcoma, other hemangioendotheliomas) vascular lesions.

References:
1. Fanburgh-Smith JC, Michal M, Partanen TA, Alitalo K, Miettinen M. Papillary intralymphatic angioendothelioma (PILA): a report of twelve cases of a distinctive vascular tumor with phenotypic features of lymphatic vessels. Am J Surg Pathol 1999; 23(9): 1004-1010.

2. Dabska M. Malignant endovascular papillary angioendothelioma of the skin in childhood. Clinicopathologic study of 6 cases. Cancer 1969;24:503-510.

Case 35

Franco Rongioletti
Caterina Ferreli

DIAGNOSIS: CIRCUMSCRIBED PALMAR HYPOKERATOSIS

Clinical Summary:
A 63-year old woman, without any relevant medical history, presented with an asymptomatic, slowly enlarging, depressed lesion, with a slightly erythematous base, irregular well-defined border, of 1.5 cm diameter, located on hypothenar eminence of her left palm since 15 years. The dermatoscopy showed a depressed lesion with an erythematous base and keratotic borders.

Microscopic Features:
Histopathology revealed an orthokeratotic stratum corneum with a sharp stair between the normal acral skin where there was a thick stratum corneum and markedly thin stratum corneum of adjacent involved skin. The stratum corneum was orthokeratotic and no parakeratosis was seen. Slight dilatation of the dermal superficial vessels was noted with poor or absent lymphocytic infiltrate. There was no evidence of cornoid lamella or significant keratinocyte atypia. Corneocytes of the upper layers showed no signs of vacuolization.

Discussion:
CPH is characterized by a well-demarcated annular depressed erythematous lesion on the thenar orhypothenar eminences of the palms and sole, and its distinctive histopathological features are an abrupt decrease in the thickness of the corneal layer and hypogranulosis in the affected lesion
Circumscribed palmar or plantar hypokeratosis (CPH) is a rare skin condition, that is diagnosed by its clinical manifestations, anatomical site and histopathological features. Clinically, CPH is characterized by a solitary, well-demarcated, depressed, erythematous patch, surrounded by slightly elevated and ridged borders. Multiple lesions have been rarely reported. It typically develops on the palms (mainly the thenar and hypothenar eminences) and less commonly on the soles of middle-aged to elderly women. Histologically, the epidermis is depressed with a diminished ortokeratotic stratum corneum. There is an abrupt ridge of hyperkeratosis at the transition from normal surrounding skin, and this represents the diagnostic pathological clue of CPH. The aetiology of CPH remains unclear, although several mechanisms have been proposed, including acquired epidermal malformation, repetitive minor trauma, human papilloma virus 4 infection and clonal expansion of aberrantly differentiated keratinocytes. Treatment with topical steroids and keratolytic agents results in limited benefit. Cryotherapy, photodynamic therapy and topical calcipotriol have been tried with complete or partial resolution in some cases. Rarely, spontaneous resolution can also occur.

References:

1. Perez A, et al. J Am Acad Dermatol 2002; 47: 21–7.

2. Blanco-Barrios S,et al. Am J Dermatopathol. 2011;33):e21-3

3. Boffa MJ,et al.J Eur Acad Dermatol Venereol. 2007;21:420-1

Case 36
Ed Rytina

DIAGNOSIS
NECROTISING INFUNDIBULAR CRYSTALLINE FOLLICULITIS (IN A SOLAR KERATOSIS)

Clinical Summary:
An 83 year old man with a 12mm nodule on the scalp, of uncertain duration, with an adjacent keratotic area. The nodule was an atypical fibroxanthoma. The sections are from the adjacent skin.

Microscopic Features:
There is a solar keratosis in which there is marked hyperkeratosis. There are dilated, crateriform invaginations of epidermis, probably related to follicular ostia. The keratin shows parakeratosis and contains and contains numerous yeasts and bacteria, an acute inflammatory cell exudate with a lightly eosinophilic, crystalline material. There is focal necrosis and acute inflammation of the infundibular epithelium.

Discussion:
Necrotising infundibular crystalline folliculitis is a rare dermatosis described on the head and back, most commonly on the forehead. In most cases, the keratotic invaginations can be related to hair follicles and contain birefringent, needle-shaped crystals, yeasts and bacteria. The crystals are made up of organic material and are thought to be the result of a complex interaction between the microorganisms and degenérate corneocytes.

The clinical presentation may be as waxy papules or the findings are recognised incidentally during histological examination, often associated with epidermal neoplasia or acne. The crystals are associated with infundibular necrosis and acute follicular inflammation. A few cases are reported to resemble a perforating disorder, without a definite association with hair follicles.

Resolution occurs with topical or systemic antimycotic treatment.

References:
1. Necrotizing infundibular crystalline folliculitis: a clinicopathological study. Denisjuk N *et al*. J Am Acad Dermatol. 2012 May;66(5):823-6.

2. Necrotizing Infundibular Crystalline Folliculitis Manifesting as a Perforating Mucinosis: A Case Report. Garth R. Fraga *et al*. Am J Dermatopathol 2013;35:757–760.

Case 37

Angel Santos-Briz

DIAGNOSIS: MELANOCYTIC NEVUS WITH HOMOGENTISIC ACID IN A PATIENT WITH ENDOGENOUS OCHRONOSIS (ALKAPTONURIA).

Clinical Summary:
M68. Cutaneous excision, face, BCC?

Microscopic Features:
Histologically, the lesion showed an intradermal melanocytic nevus with typical features. Moreover, crescentic, vermiform, or banana-shaped deposits of ocher-colored pigment could be identified among the melanocytic nests and inside giant multinucleated cells.
Further clinical investigation revealed a history of alcaptonuria with intense axial joint involvement, focal hyperpigmentation of both sclerae and a bluish tone of the cartilage of the ears.

Discussion:
Alkaptonuria, also called endogenous ochronosis, is a rare autosomal recessive disorder in which the hepatic and renal enzyme homogentisic acid oxidase is absent by mutation of the chromosome 3q13. The homogentisic acid oxidizes and accumulates in the tissues forming polymers and generating deposits of pigment. There is a bluish-black pigmentation of the face, neck, dorsum of the hands and palmoplantar region and bluish discoloration of the sclerae and of the cartilage of the ears and sometimes of the nose. In the joints, the deposits produce a degenerative arthropathy. Histologically, ocher or yellowish irregular deposits are observed, with crescent, worm or banana shape. The differential diagnosis is established with exogenous ochronosis, a term used for the deposition of similar hydroquinone derivatives in certain exogenously induced conditions. Although generally secondary to the topical application of hydroquinone bleaching creams in black races, it may also be produced by the oral administration or intramuscular injection of antimalarial drugs. The accumulation of ochronous pigment in a melanocytic nevus has only been described once in the literature. It has been proposed that the presence of melanocytes is necessary for the deposit of ochronous pigment, as it does not occur in areas of hydroquinone-induced vitiligo.

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Case 38
Ursula Sass Brussels ULb

DIAGNOSIS:
ATYPICAL FACIAL NECROBIOSIS LIPOIDICA

Clinical summary:
A 42-year-old woman presented with a 5 –year history of an asymptomatic annular plaque, on the right fore-head at the border of the scalp. She had no background history of diabetes mellitus.
On dermatological examination, the plaque was more than 5 cm in diameter. It was scaly, slightly indurated and atrophic in the center, with a raised erythematous border. There was no alopecia.
Clinical diagnosis was: Morphea

Microscopic features:
Histopathological examination showed a diffuse irregular granulomatous inflammation in the mid-dermis caracterised by abundant multinucleate giant cells, between collagen bundles. Rare foci of ill-defined necrobiosis were observed. The infiltrate also contained lymphocytes and plasma cells. No well- formed granulomas were seen.
The orcein stain revealed absence of elastic fibers in the granulomatous areas and elastophagocytosis. There was no mucin deposition seen with the blue alcian stain. Special stains for fungi and mycobacteria (PAS and Ziehl-Neelsen) were negative. Solar elastosis was noted. These features were consistent with the diagnosis of **Atypical facial necrobiosis lipoidica (AFNL).**

Discussion:
AFNL was first described by Forman in 1954. It has an unclear nosologic status and is probably a variant of annular giant-cell granuloma. It is rare and occurs mainly on sun exposed areas, affecting females in the fourth decade.
Clinical features a typical, characterized by one or more annular plaques on the upper face and scalp, which have slightly raised borders and measure 1 to 5 cm in diameter with central atrophy. Alopecia may be present. It usually develops in the absence of diabetes mellitus. Very rare patients have concomitant typical necrobiosis lipoidica on the shins.
Main differential diagnosis are granuloma annulare, sarcoidosis and necrobiotic xanthogranuloma

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Case 39

Philip E. Shapiro, M.D.

DIAGNOSIS: LICHEN PLANUS PIGMENTOSUS-INVERSUS, WITH PSEUDOMELANOCYTIC NESTS

Clinical Summary:
48-year-old Caucasian woman with several discrete brownish macules in the axilla. The clinician's impression was multiple seborrheic keratoses or warts. Evidence of lichen planus was not noted at other sites.

Microscopic Features:
There are foci of vacuolar alteration, a moderately dense lichenoid lymphocytic infiltrate, melanophages, and papillary dermal fibrosis. The epidermis is atrophic in some areas; it is slightly hyperplastic with a jagged undersurface and slight hypergranulosis and hyperorthokeratosis elsewhere. At the dermal-epidermal junction, there are a few nests of cells with small nuclei.

Discussion:
Lichen planus pigmentosus, described by Bhutani et al. from New Delhi in 1974, is generally regarded as a variant of lichen planus and distinct from erythema dyschromicum perstans, though this remains controversial. It has been reported predominantly in darker-skinned individuals, particularly from Asia, and is characterized by gray-brown macules and patches on sun-exposed areas, particularly the face and neck, without accompanying erythema. It is asymptomatic to mildly itchy. Histologically, there are vacuolar alteration, melanophages, and a perivascular and occasionally lichenoid infiltrate, usually without the dense band-like infiltrate typical of lichen planus. Hyperkeratosis and epidermal atrophy are sometimes seen. Lichen planus pigmentosus-inversus is a variant of lichen planus pigmentosus that was first described by Pock et al. from the Czech Republic and is characterized by a predilection for intertriginous areas, particularly the axilla. In Caucasians, it seems to be more common than ordinary lichen planus pigmentosus.
The first publication describing **pseudomelanoctyic nests** was by Maize et al. in 2003. They described an Indian man with multiple brown macules on the temple, biopsy of which revealed nests of cells at the dermal-epidermal junction that resembled melanocytes, leading to an initial erroneous impression of regressing malignant melanoma in situ. The confusion was exacerbated by Melan-A positivity in the pseudomelanocytic nests. Further clinical correlation and immunostaining (e.g., negativity with other melanocyte markers) ultimately led to the realization that the patient's disease was inflammatory, not melanoma. Additional published reports (and numerous anecdotes) have highlighted this histopathologic pitfall, in which these pseudomelanocytic nests can lead to an erroneous diagnosis of melanoma. Lichen planus pigmentosus is probably the inflammatory process with the greatest predilection to form these pseudomelanocytic nests, while lichen planus-like keratosis is the disease in which they are encountered most frequently. Keys to avoiding the pitfall are awareness of the phenomenon and clinical correlation, but the latter can be particularly challenging when the lesion is solitary. The following histologic features can aid in identifying nests as pseudomelanocytic, rather than truly melanocytic:

- There is not other evidence of a melanocytic neoplasm (e.g., a proliferation of solitary melanocytes).
- The nests contain cells with small nuclei with condensed chromatin.
- The nests may appear to contain a mix of cells, including necrotic ones.
- The specimen shows additional histologic features of a non-melanocytic process.
- Immunoperoxidase stains can be helpful but are usually not necessary and can be misleading.

Warning: Melanoma may have a lichenoid infiltrate and simulate a lichen planus-like keratosis.

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Lichen planus pigmentosus

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Psuedomelanocytic nests

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Case 40
Prof. Christopher R. Shea, MD

DIAGNOSIS
ERYTHEMA DYSCHROMICUM PERSTANS

Clinical Summary:
An Hispanic female (skin type IV) born in Puerto Rico, who described her ancestry as Hispanic, Jewish, and Nigerian, presented to clinic with a one-year **history** of gray-brown, symmetrical patches on upper extremities, neck, abdomen, and thighs. This condition first began after working in her garden, approximately one year before initial visit, as an itchy rash confined to the left dorsal arm. Subsequently she noticed gray-brown discoloration on both dorsal and ventral forearms, with subsequent spread to the face, neck, chest, abdomen, and legs. Except for local pruritus in the initial lesion, she denied any associated symptoms. She thought that bread and sunlight might be trigger factors. **Past medical history** included strokes in 1996 and 2011. She had been taking aspirin for this condition but stopped it shortly before her initial visit, concerned that it might be contributing to her rash. She denied any family history of skin conditions. She worked as a nurse. On **physical examination**, multiple grey-brown, round to oval patches were distributed symmetrically on the ventral and dorsal surfaces of the distal upper extremities, chin, anterior neck, abdomen, anterior thighs, and a few were scattered on the distal aspect of both legs. The right dorsal hand had a similar, grey-brown patch, but notably was surrounded by a slightly raised, thin, erythematous border (biopsy site). Lesions were less prominent when viewed with Woods light.

Microscopic Features:
There is vacuolization of the epidermal basal layer and individual keratinocyte apoptosis. A perivascular lymphocytic infiltrate and scattered melanophages are present in the superficial dermis. The periodic acid-Schiff stain is negative for fungi or significant basement membrane thickening. The colloidal iron stain demonstrates normal amounts of dermal mucin.

Discussion:
EDP (dermatosis cenicienta, ashy dermatosis, erythema chronicum figuratum melanodermicum) is an idiopathic dyspigmentary disorder characterized by blue-gray cutaneous macules. Most reports concern patients from Central and South America and Asia; a large series from Korea has recently been published. The etiology is unknown; exposure to putative pathogenic factors (ammonium nitrate, parasites, X-ray contrast material, etc.) has been suggested to trigger an abnormal response in cell-mediated immunity. The **histopathology** exhibits vacuolization of the epidermal basal layer, pigment incontinence, and a perivascular lymphohistiocytic infiltrate; colloid bodies are occasionally seen. However, identification of active interface dermatitis requires precise biopsy of the active, peripheral, red border, which is not evident in all lesions; otherwise, the only histopathologic finding may be dermal melanophages. The **differential diagnosis** includes other interface dermatitides including, especially, lichen planus pigmentosus (LPP). Some authors do not accept that these two names represent truly distinct entities and, indeed, some patients have been described with features of both conditions. However, while the histopathologic resemblance of the two conditions is considerable, they can usually be distinguished on clinical grounds. Thus, EDP classically presents as asymptomatic, gray-blue, hyperpigmented patches with an elevated

erythematous border in their early stages, symmetrically distributed on the face, torso, and upper extremities. In contrast, LPP typically affects the face and flexural body folds, is pruritic, may have darker pigmentation, and lacks an active border. Furthermore, EDP does not involve mucosae, whereas LPP reportedly may do so. **Treatment** of EDP is usually disappointing. As with most cases, our patient's condition has proved unresponsive to mid- and high-potency topical steroid therapy. Clofazimine and dapsone have been suggested as a potentially helpful treatment in some cases.

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Case 41
Dr Manuraj Singh

DIAGNOSIS
FIBROADENOMA OF VULVA WITH LACTIFEROUS CHANGE.

Clinical Summary:
35 year old female with ? vulval cyst, two weeks post partum.

Microscopic Features:
The sections show a circumscribed but unencapsulated biphasic lesion with epithelial and stromal components. The epithelial element is composed of glands and irregularly-shaped spaces lined by an epithelial-myoepithelial bilayer. There is focal epithelial proliferation without atypia. In areas, the epithelial cells show secretory cytoplasmic changes which are presumably attributable to the recent pregnancy. The stroma is composed of bland fibrous tissue and there is no undue mitotic activity. There is no overt leaf-like architecture or stromal condensation.

The appearances are those of a fibroadenoma showing focal lactation changes. Fibroadenoma is uncommon at this site but it is well described and thought to arise from anogenital mammary-like glands.

Discussion:
There is a diverse range of benign and malignant lesions involving the anogenital mammary-like glands which have a striking similarity to their mammary counterparts. These include lactating adenoma, hidradenoma papilliferum, fibroadenoma, phyllodes tumour, extramammary Paget's disease and mammary-type ductal and lobular carcinoma.
In addition, a recent paper has shown similar molecular mutations between these lesions and their mammary counterparts. Relevant immunohistochemical findings will be discussed during the actual presentation.

References:
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Case 42
Luís Soares de Almeida

DIAGNOSIS
Metastasis: Thyroid

Clinical Summary:
69 year old female, 1-month evolution of a soft and painful nodule on the scalp. History of breast carcinoma 16-y before.

Microscopic Features:
Intradermal uncapsulated nodule of clear epithelioid cells displayed in tubular and trabecular pattern embedded into a hemorrhagic stroma, with no inflammatory infiltrate. Necrosis was absent but mitotic figures abounded. Focal deposits of a colloid-like substance, surrounded by polygonal neoplastic cells, were observed.

Discussion:
Our diagnosis was cutaneous metastasis. Concerning the origin, we thought of kidney, regarding the clear cell and highly vascularized nature of the neoplasm; breast, due to previous history; lung, regarding the tubular pattern; and thyroid, taking into account not only the cytological aspects but also the eosinophilic-staining colloid.
Hence, immunostains were performed as follows:
1) CK7 positive and CK20 negative, excluded nephrological origin;
2) GATA-3 negative, excluded breast origin;
3) TTF-1 was negative, discarded a primary lung neoplasm;
4) Vimentin and thyroglobulin positivity confirmed the diagnosis of cutaneous metastasis of thyroid (papillary) carcinoma.

References:
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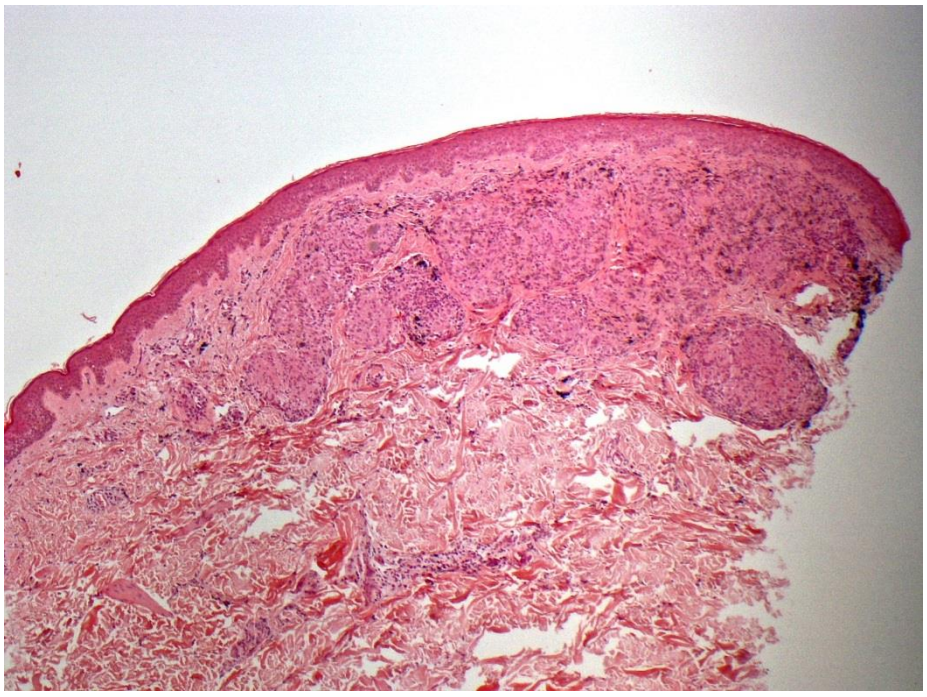
Case 43

Susanna Szakacs

DIAGNOSIS:
SARCOIDOSIS PRESENTING AS TATTOO REACTION

Clinical Summary:
The patient was a 33 year old woman who presented with asymptomatic papules and plaques within the black areas of a long standing tattoo on her back. Around the same time she also noticed tender nodules on her forearms. She had no history of any illness or infection, apart from erythema nodosum 7 years previously, which had resolved spontaneously.

Microscopic Features:
The punch biopsy shows nests of non-caseating epithelioid granulomata associated with black tattoo pigment in the superficial and mid dermis. There is only a sparse lymphocytic infiltrate around the nests. The epidermis is not involved. Special stains for infective organisms (PAS, Grocott, Ziehl-Neelsen, Wade-Fite) were negative.



Discussion:
Exogenous pigments introduced into the skin with tattoos have been associated with a rising incidence of various dermatoses (e.g. allergic contact dermatitis, lichenoid dermatitis, photo induced reactions, granulomatous, sarcoidal and pseudolymphomatous reactions). The nature of these reactions appears to depend on the pigment type, the induced immunologic process and the site.

In this case, a second biopsy from the nodules on the arm and additional clinical investigations confirmed the diagnosis of sarcoidosis. It was of interest that two months later the nodules

spontaneously regressed, prior to treatment and further investigations. This coincided with the patient discovering that she was pregnant.

It is important for both dermatologist and pathologist to be aware of cutaneous sarcoidal tattoo reaction as a potential marker of systemic disease.

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   J Post, P Hull
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   J Cutan Med and Surg 2008, 12(1):43-48

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Case 44
Saleem Taibjee

DIAGNOSIS:
CHRONIC RADIATION DAMAGE RESULTING FROM REPEATED CARDIAC CATHETERISATIONS

Clinical Summary:
82-year-old male, non-healing lesion excised from the right upper back, the clinical diagnosis was suspected basal cell carcinoma.

The initial histological impression (see below) was of radiotherapy-related change. However, after reviewing the patient's previous medical history, there was no history of prior radiotherapy (for cancer). Instead, the patient had a complex co-morbidity including ischaemic heart disease, diabetes mellitus, and chronic renal impairment. He had undergone multiple previous interventional cardiology procedures (including coronary artery stenting/angioplasty) in the period from 1986 to 2013. Calculated retrospectively, the estimated resulting cumulative dose to the skin was 18Gy.

Microscopic Features:
Large ulcer lined by fibrin, unremarkable adjacent epidermis. Deep to the ulcer the dermal collagen is strikingly sclerosed / hyalinized, with vascular proliferation, and on closer scrutiny there are 'atypical' stellate fibroblasts as often seen in radiotherapy-related change. Minimal inflammation.
Elastic-van-Gieson stain shows loss of elastic fibres within the hyalinized zone.

Discussion:
Radiation acquired from imaging procedures can be of sufficient cumulative dosage to cause skin sequelae, particularly since historically radiation doses were higher with older technology, and the skin may become more vulnerable to effect after each successive exposure. Risk factors include cumulative radiation dose, obesity, diabetes and connective tissue diseases. Ulcerated lesions are typically seen on the upper back which relates to the left anterior oblique or right anterior oblique positioning used in interventional cardiology. There may be a long latency, sometimes skin changes presenting months or even years after radiation exposure. Histological clues include the pattern of dermal sclerosis, telangiectasia and conspicuous stellate fibroblasts. These changes are similar to the sequelae from arising from radiotherapy treatment for cancer.

References:
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Case 45
Dr. Meera Thomas

DIAGNOSIS:
PROTOTHECOSIS

Clinical Summary:
This 18 year old male presented with history of recurrent papular rash on the face since one year and swelling of left knee since 6 months. He has been presenting with history of recurrent fever, rash, persistent anemia, eosinophilia and splenomegaly since 10 years of age when he was diagnosed to have combined T-cell and B-cell immunodeficiency.

Microscopic Features:
Shows skin and scanty superficial subcutis. The epidermis shows basketweave hyperkeratosis and focal flattening of the rete pegs. The superficial dermis shows extensive infiltration by mixed inflammatory infiltrate composed of many multinucleated giant cells, lymphocytes and histiocytes. Yeast like organisms, with thick walls 2-12 microns in size,, staining positive on Periodic Acid Schiff stain and negative with mucicarmine with broad based budding were seen. These resembled Histoplasma spp / Blastomyces dermatitidis. Eosinophilic and basophilic endosporulating spherules radiating from a central sporangiphore were also seen in the dermal infiltrate and in the giant cells.

Discussion:
Prototheco sis is an extremely rare disease caused by infection with Prototheca spp., which belong to the category of achloric algae. Prototheca are ubiquitous in nature, occurring in such environments as the slime flux of trees, water, soil, and the viscera of fish [1]. They infect by traumatic inoculation into subcutaneous tissues. Although Prototheca are widely found in nature, few cases of protothecosis have been reported worldwide (approximately 100 cases) [2]. Abnormalities in the immune status of the host are thought to be involved in the development of this disease.
It needs to be differentiated from Blastomycosis which also shows broad based budding but no morula formation. Cryptococus though it is similar in size to Protothecosis, can be differentiated by being positive on mucicarmine stains and not having a morula formation or broad based budding Coccidiodes immitis are seen as spherules containing numerous endospores measuring 5 µm to 10 µm, present either within giant cells or free in the tissue. Rhinosporidium sporangia with endospores are larger in size and have a thick chitinous wall.

The correct diagnosis can be achieved without difficulty only if the laboratory personnel are alert in observing the typical large spherical cells that show sporangiospores resembling a morula when stained with Lactophenol cotton blue (3).

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Case 46

Nick Tiffin

DIAGNOSIS:
BLUE GREEN ALGAE POISONING AFTER SWIMMING IN LAKE WINDERMERE

Clinical Summary:
The patient was admitted to the dermatology ward late Sunday night, having spent the day performing a triathlon which involved swimming in Lake Windermere. He shortly developed vomiting and a sun-sensitive, erythematous and blistering rash which later peeled. He was investigated for lupus with autoimmune screening. However, the dermatopathologist attending the ward round the next day was a Cumbrian, and familiar with the dangers of swimming in the Lake during hot spells (the preceding week had been a heat-wave). He diagnosed cyanobacteria poisoning. As expected, the rash and symptoms rapidly resolved over the next couple of days.

Microscopic Features:
Epidermis with occasional apoptotic cells and subepidermal oedema. There is a mild to moderate superficial perivascular lymphohistiocytic infiltrate accompanied by small numbers of neutrophils.

Discussion:
The diagnosis was obtained from the history; it is important not to forget the pathogenicity of some plants and other elements of the environment. The dermatopathologist's local knowledge permitted the correct diagnosis and further tests were not indicated. The histology was entirely consistent with a phototoxic reaction.

References:
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Case 47

Carlo Francesco Tomasini

DIAGNOSIS
SEPTIC VASCULITIS WITH MALAKOPLAKIA FOLLOWING ESCHERICHIA COLI SEPTICEMIA IN AN IMMUNOSUPPRESSED WOMAN

Clinical Summary:
46 year-old liver transplant female with a 5 year history of chronic
febrile cholangitis and sepsis from E.coli. Since 6 months, development of violaceous nodules and plaques on the face and acral extremities. The lesions typically occurred just after the fever had resolved and tended to persist and recur with discontinuation of antibiotic therapy. Fresh examination of tissue material taken from the base of ulcerations was negative for Entamoeba trophozoites and results of microbiologic studies were consistently negative. Significant levels of E.coli DNA fragments from skin lesions were finally and unambiguously identified by next generation sequencing technique.

Microscopic Features:
Histopathologic examinations showed widespread vascular changes affecting the dermal vessels with occlusive thrombi surrounded by sheets of macrophages with large clear cytoplasm containing variable numbers of concentrically laminated, round-ovoid basophilic bodies inclusions with pale centers. These bodies were focally PAS and von Kossa positive (Michaelis-Gutmann bodies). Subepidermal edema, perivascular haemorrhage, leukocytoclasia as well as intraepidermal pustules were also seen. High power view revealed rare macrophages containing clusters of gram negative bacteria.

Discussion:
Malakoplakia is a rare, acquired granulomatous disease usually occurring in immunosuppressed patients in which a defect of the killing capacity of macrophages after endocytosis is considered to be the central event. The disease can affect many systems but is more common in the urogenital tract and is almost invariably associated with infection with coliform bacteria, especially *Escherichia coli.* In our patient, the course of septic vasculitis associated with chronic cholangitis and E.coli septicemia was complicated by the acquired defective macrophage killing that resulted in an accumulation of bacterial degradation products and a granulomatous reaction. The discontinuation of immunosuppressive therapy associated with a sustained antibiotic therapy with quinolones - agents that concentrate in macrophages – was curative.

References:
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Case 48

Carlos A Torres-Cabala, MD

DIAGNOSIS
MELANOCYTIC NEVUS WITH PARTIAL LOSS OF BAP1 ("BAPOMA")

Clinical Summary:
A 32-year-old female presents with a 4 mm pink papule with eccentric pigment globules and dotted vessels on dermoscopy, located on her right antecubital fossa. The patient has a history of multiple basal cell carcinomas, nevi with architectural disorder and cytologic atypia ("dysplastic"), combined nevi, and nevi with desmoplastic features.

Microscopic Features:
Sections reveal a predominantly intradermal proliferation of melanocytes with biphenotypic appearance. Small melanocytes arranged in nests and as single cells (intradermal melanocytic nevus) are seen admixed with larger melanocytes with amphophilic to pale eosinophilic cytoplasm and large vesicular nuclei with prominent nucleoli (Spitzoid features). Immunohistochemical studies revealed the larger cells to be negative for nuclear BAP1, which was preserved in the standard nevus areas. BRAF V600E was positive throughout the lesion.

Discussion:
The tumor suppressor gene BRCA1-associated protein-1 (*BAP1*) is a potent modulator of carcinogenesis. Mutations leading to loss of BAP1 expression increase susceptibility to multiple tumors such as uveal melanoma, cutaneous melanoma (including blue nevus-like melanoma), mesothelioma, clear cell renal cell carcinoma, and basal cell carcinoma, among others. Melanocytic BAP1-mutated atypical intradermal tumors (MBAITs) or "BAPomas" clinically present as small tan/pink papules. These lesions commonly show a biphasic appearance, as seen in this case. A lymphocytic infiltrate associated with the larger Spitzoid cells can be present. Recognizing these lesions is of great importance, especially if multiple, for adequate genetic counseling of these patients and their families. Immunohistochemistry for BAP1 should therefore be performed as a screening test in those lesions with morphological features of "BAPoma".

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Case 49

Esmeralda Vale

DIAGNOSIS
PRIMARY CUTANEOUS EWING SARCOMA

Clinical Summary:
32-year-woman who presented to the Dermatologist with a dome-shaped, pink tumor, very well circumscribed, on the left heel. The lesion had 1,2 cm of diameter and had months of evolution and was asymptomatic.
The clinical diagnosis was Eccrine poroma.

Microscopic Features:
The histopathologic examination revealed a very well circumscribed tumor, surrounded by a collarette, occupying all the dermis and focally invading the superficial part of the subcutaneous tissue. It was composed by sheets of uniform, small, blue, round cells which had round nuclei, finely dispersed chromatin and one nucleolus. A prominent mitotic activity was present as well as numerous mitosis.
The tumoral cells were negative for melanocytic, epithelial, neuroendocrine markers and showed strong membranous positivity for CD99 and FISH revealed a rearrangement of the EWSR1 gene at chromosome 22q12.

Discussion:
This is a rare case of Primary cutaneous Ewing sarcoma. It was first recognized by Angervall and Enzinger in 1975. It shows a young female predilection and the lower extremities the most frequent location, however there are rare cases located on the foot. It is associated with an indolent course, less aggressive behavior and has a more favorable prognosis.
Histologically it belongs to the group of cutaneous small blue round cells tumor. The main histopathologiacl differential diagnosis is with Metastatic Ewing sarcoma. The absence of systemic involvement (MRI and CT scan negative) confirmed the diagnosis of Primary cutaneous Ewing sarcoma.
The presence of membranous expression of CD99 and EWSR1 translocation are important in the differential diagnosis with several other small blue round cell tumors, like Merkel cell carcinoma, Lymphoblatic lymphoma, Metastatic small cell carcinoma, Metastatic neuroblastoma and Synovial sarcoma.
The current recommendations for the treatment of both Primary cutaneous Ewing sarcoma and bone Ewing sarcoma are the same, although some authors suggest a less intensive chemotherapy regimen for these cases of Primary cutaneous Ewing sarcoma.

References:
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Case 50

Isabel Viana

DIAGNOSIS: AFRICAN HISTOPLASMOSIS

Clinical Summary:
A 79-year-old male was sent to the Dermatology department because of an asymptomatic ulceration on the right thigh for 6 months. The lesion started as a pustule with slow evolution to a 2 cm ulcer with raised borders and a surrounding hyperpigmented halo.
The patient was known to be HIV-2+ for two years and was diagnosed AIDS and pulmonary tuberculosis one year ago, being under antiretroviral and tuberculostatic therapy since then which he accomplished irregularly. He was a war veteran, having lived in Guiné-Bissau and Angola 40 years ago. In his past history a diagnosis of neurosyphilis was also relevant.

Microscopic Features:
The biopsy showed a superficial ulceration with underlying granulomatous infiltrate, with dispersed lymphocytes, plasma cells and neutrophils and many multinucleated giant cells; these contained several ovoid, lemon-shaped yeasts, measuring 7-8 □m ,with a single nuclei, that where highlighted by PAS and Grocott stains; Mucicarmine was negative; some narrow-budding structures could be identified.
The morphologic features were very suggestive of Histoplasma capsulatum var. duboisii and the diagnosis was confirmed by mycologic exam and sequencing of genomic DNA.

Discussion:
Histoplasma capsulatum is a dimorphic fungus: it has a mycelium form in the soil, at room temperature and a yeast form in the tissues. It has two main variants: Histoplasma capsulatum var. capsulatum responsible for the so-called American Histoplasmosis and Histoplasma capsulatum var duboisii implicated in African Histoplasmosis. They differ in size, (having the former a 2-4 □m diameter and the last one 7-15 □m), geographic distribution and clinical manifestations. Histoplasma capsulatum var. capsulatum has a worldwide distribution but Histoplasma capsulatum var duboisii is restricted to sub-Saharan Africa and Madagascar; cases occurring outside these areas are usually imported. While American Histoplasmosis has a course similar to tuberculosis with frequent pulmonary involvement, African Histoplasmosis affects mainly the skin, lymph-nodes, bone and internal viscera. It may occur has a solitary localized lesion or in a disseminated form. In the skin, lesions appear as nodules, abscesses and ulcerations with frequent involvement of subcutaneous tissue and underlying bone. Pulmonary involvement is rare as is co-infection with HIV.
African histoplasmosis is a rare disease and a prolonged contact with the organism seems to be necessary; late reactivation is frequently observed as was the case of our patient, probably triggered by imunosupression.

From the histological point of view the main differential diagnosis is with Blastomycosis where organisms with similar size are nevertheless multinucleated and have a broad-based budding opposite to the narrow-based budding of Histoplasma capsulatum var.duboisii. In Cryptococcosis a mucoid capsule highlighted with mucicarmine is characteristic.
Nevertheless other complementary exams are necessary to confirm the diagnosis, being nowadays PCR the most important method used to identify the organisms implicated in these infections.

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