Self-Assessment
Answers Cases 16 - 26

Chairs:
Richard Carr (UK)
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# Self-Assessment Answers

**Part 2 – Saturday 30th September 2017**

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Case 16
Ruth Green

DIAGNOSIS:
CRYOglobulinaemia

Clinical Summary:
This 61 year old man presented with a 9 month history of a purpuric rash involving the dorsal limbs and feet. He had developed ulceration of the feet, posterior knees and dorsal right hand requiring hospital admission for analgesia. He described episodic joint pains for several years and intermittent fatigue. He had a past medical history of hypertension which was controlled with medication.

Microscopic Features:
Densely eosinophilic material in lumina of dermal blood vessels.
Dermal vascular proliferation.
Mild perivascular mixed inflammatory cell infiltrate.
Red blood cell extravasation.
Focal leukocytoclastic debris.

Discussion:
The eosinophilic material stained positive for Periodic acid-Schiff (PAS) +/- diastase, consistent with a diagnosis of cryoglobulinaemia.
Subsequent investigations confirmed the presence of monoclonal IgG kappa within the patient’s blood, consistent with type I (monoclonal) cryoglobulinaemia. The cutaneous lesions (and joint symptoms) resolved with a reducing course of oral prednisolone but recurred after this was discontinued. Further investigation and management by renal medicine and haematology physicians is pending.

Cryoglobulins are immunoglobulins that reversibly precipitate and redissolve in the blood dependent on temperature. As the concentration increases, precipitation can occur at higher temperatures, and can result in clinical symptoms and signs. Cutaneous manifestations are common, most frequently purpura, and are often the presenting complaint.

Cryoglobulinaemia is typically divided into 3 categories according to the Brouet classification. Type I is related to monoclonal immunoglobulins only and often associated with an underlying lymphoproliferative condition. This category shows the classic eosinophilic hyaline deposits within blood vessels on skin biopsy, as seen in this case. In the ‘mixed’ types (II and III), features of an acute leukocytoclastic vasculitis can be more typical. Mixed cryoglobulinaemia is commonly associated with hepatitis C as well as other underlying systemic conditions including connective tissue disease, lymphoproliferative conditions and infection.

References:
Case 17
Marc Haspeslagh

DIAGNOSIS:
EPIDERMAL TYPE OF PANFOLLICULOMA

Clinical Summary:
Papillomatous tumor frontal left in male 84 years

Microscopic Features:
Intraepidermal plaque like tumoral lesion with upper and lower hair follicle differentiation.

Discussion:
Four types of panfolliculoma are described: nodular, epidermal, cystic and endophytic resembling a hair follicle.
Of this epidermal type has only 17 cases have been described. The male female ratio is 12/5, with predeliction for the legs and forehead. The tumor shows infundibular, isthmic, inner and outer rooth, matrical and germinative differentiation and probably forms the end of a spectrum of many other epidermal neoplasms with follicular differentiation such as reticulate acathoma, reticulate acanthoma with sebaceous differentiation, superficial benign proliferation with sebaceous differentiation, superficial benign proliferation with multiple differentiation, pilomatrical horn, outer rooth sheath acanthoma and tumor of follicular infundibulum.

References:
1. Panfolliculoma and histopathologic variants: a study of 19 cases
   Shi-Jun Shan and Ying Guo Am j Dermatopathol 36;12 965-971 2014
2. Epidermal Panfolliculoma: a report of 2 cases
   A Harris et al Am j Dermatopathol 33;1 e7-e10 2011
3. Panfolliculoma with an endophytic architecture resembling a hair follicle: report of three cases
   V Terushkin et al J cutan Pathol 43;1074-1076 2016
Clinical Summary:
Biopsy proven SCC (fungating). Centrally tumour through to fascia.
Excised 1cm margin, down to fascia.

Microscopic Features:
This is a collision tumour with the predominating tumour being a moderately differentiated Squamous cell carcinoma. A separate tumour is seen close to the squamous cell carcinoma as an ulcerated lesion connected to the epidermis and having a lobular architecture. The tumour cells consist of immature cells with variable cytological atypia and brisk mitotic activity. In areas there is a squamoid appearance with prominent keratinization with formation of ghost cells. These lobules are extensively colonized by melanocytes (confirmed by immunostains).

Discussion:
This is a collision tumour with a Melanocytic matricoma in close association with a squamous cell carcinoma. Melanocytic Matricoma are tumours originating from a follicular lineage and are regarded as malignant tumours and in general experience their behavior is low grade malignant.

References:
Case 19
Jacqueline M. Junkins-Hopkins MD

DIAGNOSIS:
ANGIODESTRUCTIVE LYMPHOMATOID PAPULOSIS

Clinical Summary:
Her past medical history is unremarkable. Her review of symptoms was remarkable for GI complaints, for which she was referred to a gastroenterologist. The work up was reportedly normal. The lesion cleared without treatment, less than two months after the onset.

Microscopic Features:
This punch biopsy shows extensive necrosis of the dermis, and subcutis, associated with ulceration and perforating collagenosis. Adjacent epidermis is mildly acanthotic, without evidence of excoriation or significant necrosis. There is a superficial and deep infiltrate of mononuclear cells, including atypical and non-atypical lymphocytes, neutrophils, and eosinophils. These are also identified in the necrotic foci. There is vascular necrosis. A CD30 stain was positive in atypical lymphocytes within and around the vessel wall. Areas of necrosis showed faint positivity of degenerating lymphocytes. Granulomas and plasma cells were absent. Stains for organisms were negative. EBER was negative.

Discussion:
Lymphomatoid papulosis (LyP) is defined as a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of lymphoma, in particular, lymphoma with a CD30 positive immunophenotype, such as anaplastic large cell lymphoma (ALCL). The latter presents with tumors (typically >2cm) and plaques, that persist, or only partially regress.

LyP, together with primary cutaneous ALCL, and borderline lesions, are recognized by the WHO-EORTC cutaneous lymphoma classification, under the spectrum of primary cutaneous CD30+ lymphoproliferative disorders (LPDs). The “spectrum” aspect of LPDs is stressed and highlighted by the fact that LyP and ALCL may have histopathologic features that overlap so greatly that only the clinical presentation distinguishes the two from one another. This is especially the case when the lesions of LyP contain sheets of the atypical CD30 positive cells similar to that seen in ALCL.

The lesions of LyP are usually under 1-2 cm, although some lesions may reach a diameter closer to 2cm, especially if there is prominent angioinvasion and necrosis, similar to this case. Usually the lesions arise as small dermal papules that quickly progresses to a stage in which there is central crusting, scaling, and/or necrosis, as the lesion evolves. Eventually, there is complete and spontaneous resolution of the lesion, often resulting in post-inflammatory changes, or at times pox-like scarring. The clinical lesions may simulate recurrent folliculitis or insect bite reactions (initial lesions), especially if there is pruritis that may sometimes accompany the lesions. Any location may be affected; regional disease may also occur.

Histologically, LyP is characterized by a lymphocytic infiltrate that follows the vascular plexus, with extension into the interstitium and epidermis, imparting a wedge-shaped appearance to the scanning silhouette. The epidermis is usually acanthotic, with varying
degrees of alteration, depending on the area and stage of the lesion biopsied. There may be marked epidermotropism, scale crust, spongiosis, necrosis, or ulceration. The histopathologic features of the infiltrate also vary, and these presentations have been referred to as Types A, B, C, D, and E LyP. Type A is the most classic, and is characterized by a mixed infiltrate of small lymphocytes, neutrophils, eosinophils, and an admixture of large atypical CD30+ lymphocytes, often with prominent nucleoli or with Reed-Sternberg-like nuclei. The CD30 cells are scattered singly and in small clusters. The biopsy of this woman showed some of these features, including atypical lymphocytes admixed with neutrophils and eosinophils. The infiltrate of Type B is comprised mostly of lymphocytes with small irregular or cerebriform nuclei, demonstrating prominent epidermotropism similar to mycosis fungoides. This is differentiated by the wedge-shaped architecture of the infiltrate and clinical presentation of recurring papules instead of persistent patches and plaques. These cells may not express CD30. Type C may be indistinguishable from ALCL, as it contains sheets of large atypical CD30+ cells (often the entire tumor contains these cells). Type D is recently “named”, and presents as a markedly epidermotropic infiltrate of atypical lymphocytes. While the immunophenotype may be quite variable in LyP (CD4+/CD8-, CD8+/CD4-, CD4-/CD8-), that of LyP D is CD8+ and expresses cytotoxic proteins (TIA-1, Granzyme B, perforin); thus, needs to be differentiated from the aggressive cytotoxic cutaneous lymphomas (Extranodal NK/T-cell lymphoma, nasal type and Berti’s lymphoma, or CD8+ aggressive epidermotropic cytotoxic TCL).

LyP may also be associated with vascular invasion and destruction. These angioinvasive presentations have also recently been characterized and are referred to by some as Type E LyP. The biopsy you reviewed showed marked vascular and tissue necrosis, and based on the history of recurrent lesions that evolve through an ulceronecrotic stage prior to self-healing, the changes are felt to best represent this subtype.

The differential diagnosis of the angioinvasive presentation of LyP includes angiodestructive lymphomas, especially those that express EBER (Epstein-Barr Virus), including extranodal NK/T-cell lymphoma, nasal type and EBV positive B cell lymphomas, as well as immunosuppressive-related disorders. These and other cutaneous lymphomas that may show necrosis, such as gamma delta lymphoma, need to be differentiated from LyP by the clinical presentation of non-resolving plaques and tumors, and by characteristic immunophenotypic features in the latter, such as gamma delta positivity.

Vasculitis due to rheumatologic disease would not typically have atypical cells that are CD30 positive. Infectious causes, especially virally-induced (herpes, molluscum), frequently show overlap with LyP, due to the presence of activated T cells that express CD30. Viral cytopathic changes should be evident. Herpes lesions may show quite a bit of clinical overlap, including evolution through a necrotic and self resolving stage, but the lesions of herpes simplex tend to recur in the same location as blisters on an erythematous base, not as crops of papules, as is the case with LyP. Other infections, including fungal, may also show CD30 lymphocytes. Therefore, one should exclude an infectious process prior to making a diagnosis of LyP.

References:
Case 20

Laszlo J Karai, MD, PhD

DIAGNOSIS:
LYMPHOMATOID PAPULOSIS WITH 6P25.3 REARRANGEMENT

Clinical Summary:
A 75-year-old male presented with an ulcerating tumor on his left upper arm. The clinical impression was pyogenic granuloma. The patient does not have history of autoimmune condition, and neither of chronic immunosuppressive drug use, such as methotrexate.

Microscopic Features:
Sections show a nodular lymphoid infiltrate showing prominent pagetoid lymphocytosis of the epidermis. The atypical cells are small to medium in size and present in a perieccrine, perifollicular distribution. Areas showing perivascular distribution can be also seen. Significant nuclear hyperchromasia with irregular nuclear out lines evident with small amount of cytoplasm. Frequent mitotic figures and apoptotic bodies are evident, however, there is no evidence of tumor necrosis.

Discussion:
Lymphomatoid papulosis (LyP) is an indolent cutaneous lymphoproliferative disorder with clinical and pathologic features overlapping those of both reactive conditions and aggressive lymphomas. The clinical, histopathological, immunophenotypic, and genetic characteristics of lymphomatoid papulosis with 6p25.3 rearrangement are unique and allow differentiation from other types of LyP. Lesions are typically affecting elderly patients with the mean age being 75 years. Clinically the tumors are localized to a single anatomic area and the clinical presentations suggests the differential diagnosis of benign inflammatory dermatoses or low-grade epithelial tumors. Histologically, lesions show a biphasic growth pattern, with small cerebriform lymphocytes in the epidermis and larger transformed lymphocytes in the dermis. All tumors exhibit a T-cell immunophenotype. The pathologic features raise the possibility of an aggressive T-cell lymphoma, such as transformed mycosis fungoides. However, no patient developed disseminated skin disease or extracutaneous spread. Untreated lesions regress spontaneously. These cases harbor a unique chromosomal rearrangement of the DUSP22-IRF4 locus on 6p25.3. The presented case emphasizes the importance of clinicopathologic correlation, incorporating molecular genetic analysis when possible, during the evaluation of cutaneous lymphoproliferative disorders.

References:

Case 21
Dr Sujay Khandpur

DIAGNOSIS:
FOCAL DERMAL HYPOPLASIA OR GOLTZ SYNDROME

Clinical Summary:
A 2-year old girl presented with linear hypopigmented atrophic macules with few telangiectasia, over lower back, buttock and left flank, since birth. There was no systemic anomaly.

Microscopic Features:
Flattened epidermis with effacement of rete ridges, thinned out dermis and normal subcutaneous fat lying very close to the epidermis due to significant hypoplasia of the intervening dermis. Features suggestive of focal dermal hypoplasia

Discussion:
Focal dermal hypoplasia syndrome or Goltz-Gorlin syndrome is a multisystemic X-linked dominant disorder, with involvement of the skin, ophthalmic, musculoskeletal, dental, urogenital, cardiovascular, CNS and gastrointestinal systems. Mutations in the PORCN gene on the X chromosome that regulate embryonic development, have been identified. Inactivation of one X chromosome in females causes skin lesions to occur in a blaschkoid distribution, which manifest as either linear or whorled streaks of dyspigmentation with atrophy or tumor-like out pouchings of fat. Rarely mono-symptomatic form of disease with only skin manifestations may be the only presentation, as seen in our case.

References:
Case 22  
Dr Arti Bakshi  

**DIAGNOSIS:**  
EOSINOPHILIC DERMATOSIS OF HAEMATOLOGICAL MALIGNANCY

**Clinical Summary:**  
51/M, Diagnosed with CLL. Started on chemotherapy for progressive disease. 5 months following initiation of therapy, patient developed a polymorphic rash with papules, nodules and blisters.  
An initial punch biopsy suggested drug reaction, in view of which chemotherapy was stopped. However, this did not result in improvement of rash. Repeat deep incisional biopsy done. (Left leg)

**Microscopic Features:**  
Incisional biopsy showing dense superficial and deep dermal predominantly perivascular chronic inflammatory infiltrate, rich in eosinophils. Extension of the infiltrate into subcutaneous fat is present. The epidermis shows reactive hyperplasia with spongiosis and prominent subepidermal oedema.

**Discussion:**  
Although the histological findings are reminiscent of an arthropod bite reaction, the patient denied any history of insect bite. Given the history of CLL, a diagnosis of ‘insect bite like reaction in CLL’ or Eosinophilic Dermatosis of Haematological malignancy (EDHM) was made.  
EDHM is a rare cutaneous eruption associated with CLL, but has also been described with other haematological malignancies including mantle cell lymphoma, ALL etc. Patients usually deny any history of insect bites. The rash can occur at both exposed and non-exposed sites and may precede onset of haematological malignancy. The pathogenesis is unclear, likely related to immune dysregulation leading to altered cytokine balance and eosinophil infiltration.  
It is important to be aware of this entity to avoid misdiagnosis and mismanagement. In this patient, the correct diagnosis, lead to reinstitution of chemotherapy for progressive CLL.

**References:**  

2. Exaggerated delayed hypersensitivity to mosquito bites in chronic lymphocytic leukaemia. Weed RI. Blood. 1965 Sep;26:257-68
Case 23  
Rossitza Lazova, MD  

DIAGNOSIS:  
COLLAGENOUS AND ELASTOTIC MARGINAL PLAQUES OF THE HANDS (CEMPH)

Clinical Summary:  
Hyperkeratotic translucent papules arranged linearly on the radial aspect of the hands and fingers. The condition most commonly presents in Caucasian men aged 50 to 60 years. Patients typically are asymptomatic with plaques limited to the junction of the palmar and dorsal surfaces of the hands. Lesions begin as discrete yellow papules that coalesce to form hyperkeratotic linear plaques with occasional telangiectasia.

Microscopic Features:  
Hyperkeratotic epidermis with an avascular and acellular replacement of the superficial reticular dermis by haphazardly arranged, thickened collagen fibers. The collagen fibers are oriented perpendicularly to the epidermal surface. Intervening amorphous basophilic elastotic masses are present in the upper dermis with occasional calcification and degenerative elastic fibers.

Discussion:  
Collagenous and elastotic marginal plaques of the hands (CEMPH) is a rare disorder that is acquired, slowly progressive, asymptomatic, dermal connective tissue abnormality that is underrecognized and underdiagnosed. The differential diagnosis of CEMPH includes:

1. Two genodermatoses, which clinically resemble CEMPH  
   a. Acrokeratoelastoidosis of Costa - autosomal-dominant condition that occurs without trauma in children and young adults. Histopathology shows orthokeratotic hyperkeratosis due to an overproduction of filaggrin in the granular layer of the epidermis. The reticular dermis shows basophilic, thick, curled and fragmented elastic fibers, highlighted by Verhoeff-van Gieson stain, and dilated capillaries.
   b. Focal acral hyperkeratosis - occurs on the hands and feet predominantly in black patients. On histology, the epidermis shows a characteristic orthohyperkeratosis, moderate acanthosis, and slight hypergranulosis with no dermal involvement.

2. Chronic hyperkeratotic eczematous dermatitis  
3. Palmoplantar keratodermas include callosities and drug-related palmoplantar keratodermas such as those from arsenic exposure.

References:  
**Case 24**

*M. Llamas-Velasco*

**DIAGNOSIS:**

**ATYPICAL HAND-FOOT MOUTH DISEASE MIMICING MULTIFORME MINOR**

**Clinical Summary:**

19-year old female with a 3 day evolution eruption of papulovesicular lesions which first appeared around the mouth and frontal area and rapidly spread over the whole face, hands and foot (including also palms and soles) and superior and inferior extremities. She also had few erosions on the superior palate. She only referred having a sore throat the day before starting the eruption but no fever, cold-sore or any other clinical sign or symptom. On examination, a papulovesicular eruption affecting those areas was found. On her hands and feet, the lesions tended to present an annular shape. Exanthematic virus serologies were negative. Microarray for herpes simplex, zoster, VEB, CMV, HHV6 and HHV7 was negative. RT-PCR of blister fluid demonstrates Coxsakie virus A6 (CV-A6)

**Microscopic Features:**

Skin biopsy showed and intraepidermal blister with spongiosis and ballooning of the upper epidermis conforming a picture of reticular degeneration without cytopathic changes or nuclear inclusions. Corneum strate was preserved. Within the necrotic epidermis, lots of neutrophils are observed. Dyskeratotic keratinocytes are also seen. Slight vacuolar degeneration. Edema of papilar dermis as well as a predominantly perivascular infiltrate composed of lymphocytes and histiocytes is found.

**Discussion:**

Enteroviruses, are single-stranded RNA genome with unenvolved capsid that cause worldwide infections trasmitted by fecal-oral or respiratory route. Hand-foot and mouth disease (HFMD) is the most characteristic exanthematous disease caused by enterovirus and although numerous coxackie serotypes have been implicated, CV-A16 was the most common etiologic factor. CV-A6 previously rarely attracted attention as its infections were mild or asymptomatic until a change in its clinical phenotype reported in 2008 following the discovery of a large outbreak of HFMD associated with this type CV-A6 in Finland. Since then, CV-A6 eclipsed EV-71 y CV-16 as causative agents of HFMD. CV-A6 produces usually a different clinical picture, named as atypical HFMD, more commonly affecting patients older than 5 years, with higher fever and frequent involvement of dorsal aspects of hands and feet, calves, forearm and trunk. Oral involvement as well as palms and soles involvement is less common than in the classical HFMD. Main clinical differential diagnosis include erythema multiforme (EM), drugs eruption, impetigo contagiosum and disseminated herpes simplex infection. Histopathologically, atypical HFMD induced by CV-A6 may present a histopathological picture with confluent necrotic keratinocytes on the roof of the vesicle, neutrophils inside the vesicle and a discrete vacuolar degeneration. In dermis, a mild perivascular lymphocytic infiltrate can be observed as well as some eosinophils. Erythema multiforme (EM) is also a histopathological differential diagnosis in these patients and the presence of neutrophils within the epidermis with a relatively specific involvement of...
stratum granulosum and the upper half of the stratum spinosum is a clue to distinguish atypical HFMD from EEM. Absence of cytopathic changes help in excluding herpetic or poxvirus infection.

With this case, we want to highlight this peculiar clinico-pathological picture, sometimes difficult to demonstrate as the coxsackie variant characterization is usually performed only in reference labs.

**References:**


Case No 25  
Dr Brigid Maguire  

DIAGNOSIS:  
SEBACEOUS ADENOMA IN MUIR-TORRE SYNDROME.

Clinical Summary:  
A 65 year old woman presented to her G.P. with a warty lesion on her right chest wall. She had a history of wide local excision and axillary sampling for left-sided breast cancer in 2005, and had received post-operative chemotherapy and radiotherapy. Her most recent mammogram was normal and she was otherwise fit and well. Following the report of her skin lesion, enquiry revealed a very strong family history of gastro-intestinal malignancies. A screening colonoscopy revealed a transverse colon adenocarcinoma.

Microscopic Features:  
Histology of the excision specimen showed a well-circumscribed lesion with connection to the epidermis and a multilobular pattern made up of mature and immature sebaceous cells organized into clear zones. There was no atypia or other evidence of malignancy. Immunostains for MLH1/PMS2 were positive but there was loss of staining for MSH2/MSH6. Staining of the transverse colon tumour showed an identical pattern.

Discussion:  
Muir-Torre syndrome (MTS) is an autosomal dominant condition with a high degree of penetrance and variable expression. It combines at least one cutaneous sebaceous neoplasm with at least one internal malignancy – most commonly gastro-intestinal (~50%) or genitourinary (~25%). These may occur synchronously or metachronously in relation to the skin lesion(s). It is considered to be a phenotypic variant of the more common hereditary nonpolyposis colorectal cancer syndrome or Lynch’s syndrome.

These disorders are caused by a germline mutation in one of the DNA mismatch repair (MMR) genes involved in detecting and repairing DNA replication errors. This results in a non-functional protein and a complete loss of MMR activity. As cells replicate they accumulate DNA synthesis errors more rapidly, especially in regions of repetitive modules of base pairs, referred to as microsatellites. DNA from the tumours resulting from this mutation show microsatellite instability – gain or loss of microsatellites compared with normal tissue.

Features of cutaneous sebaceous lesions which should prompt consideration of MTS are:  
- Location outside the head and neck region.  
- Multiple lesions before 50 years of age  
- Lesions with cystic change (most specific solitary marker)  
- Keratoacanthoma-like architecture  
- Mucinous areas  
- Intra-and peritumoural lymphocytes  
- Intra- and intertumoural heterogeneity  

Also note: Multiple keratoacanthomas on sun-protected sites in a young person.
Pitfalls in immunohistochemistry (IHC) to be wary of include:

- Occasional loss of MMR staining in sporadic lesions.
- Germline MMR mutation with no protein loss giving a non-functional but antigenically intact protein.
- Sebaceous hyperplasia in MTS usually shows no protein loss.
- IHC cannot differentiate between MLH1 mutation vs somatic hypermethylation.
- Loss of IHC MSH2 protein expression but without an accompanying gene mutation may have an inherited heterozygous deletion in TACSTD1, a gene upstream of MSH2, causing heritable mosaic promoter methylation and subsequent inactivation of MSH2.

Gene mutations can be confirmed using molecular techniques. The most commonly affected MMR gene in MTS is MSH2 (~90%).

References:
Case 26
Dr Pradeep Mahajan

**DIAGNOSIS:**
URTICARIA PIGMENTOSA (MASTOCYTOSIS)

**Clinical Summary:**
Three years old male child
Multiple brown to hyperpigmented lesions scattered all over the body
Lesions mostly flat, only a few raised
Induced redness and swelling on rubbing
No blistering or flushing
General health and development normal
No lymphadenopathy or hepato-splenomegaly

**Microscopic Features:**
Punch biopsy from back lesion
Infiltrate predominantly in upper dermis
At places in proximity to DEJ
Cuboidal cells with central nucleus and cytoplasm with lightly basophilic granules
Granules stain metachromatically with toluidine blue
Basal layer hyperpigmentation
Scattering of eosinophils
Superficial oedema

**Discussion:**
Common variant of mastocytosis – urticaria pigmentosa
Generalized eruption of multiple brown black macules with a few papules
Develop wheal and flare when rubbed (Darier’s Sign)
Clinical differentials – lentiginosis, secondary syphilis, chronic urticaria, atopic dermatitis etc.
Histology - Infiltrate of cuboidal cells with central nucleus and cytoplasm having lightly basophilic granules predominantly in upper dermis
Granules stain metachromatically with toluidine blue
Basal cell layer hyperpigmentation
Clinical and histologic features of cases of Bullous Mastocytosis and TMEP highlighted

**References:**

PMCID: PMC4211494
Telangiectasia macularis eruptiva perstans: more than skin deep
Casey E. Watkins,1 Winston B. Bokor,1 Stuart Leicht,1,2 George Youngberg,1,3 and Guha Krishnaswamy1,4,5