

## IN-DEPTH REVIEWS

## Review of Instructive Cases from the Zola Cooper and Lee T. Nesbitt Seminar

Etan Marks, DO<sup>1</sup>, Leah Persad, DO<sup>1</sup>, Clay J Cockerell, MD<sup>1</sup>

<sup>1</sup>Cockerell Dermatopathology, Dallas, TX

## ABSTRACT

Histopathological examination is considered to be the gold standard for diagnosis. However, research has shown that clinical correlation with pathological examination is crucial for the appropriate diagnosis. This is especially true in dermatology/dermatopathology where several entities can appear similar under the microscope, but are vastly different with their clinical presentation and vice versa. With this in mind, we mention the Zola Cooper- Lee T. Nesbitt Seminar that was established in 1954 and is the longest free standing clinical-pathologic conference still in existence. The purpose of the seminar is to serve as an educational conference designed to promote continuous excellence in the field of clinical dermatology and dermatopathology. Herein, we present six cases that were presented at the conference which highlight the importance of the clinical-pathological correlation in the practice of dermatology.

## CASE 1

**History:** A 56 year old woman presented with a 4 month history of ulcerated plaques and nodules of the trunk and extremities (Figure 1). She complained of no “B” symptoms. She had a past medical history of fibromyalgia, depression, asthma, and hypertension. She is currently on Buspirone, Gabapentin, Losartan, Pantoprazole, and Venlafaxine.

**Physical Examination:** Scattered red papules and plaques with focal areas of necrosis and ulceration on the back of the neck, mid-back and legs.

**Histopathology:** Band-like papillary dermal lymphoid infiltrate with epidermotropism comprised of large lymphocytes with irregular nuclei. The cells stained positively for CD3

and Beta-F1, but were mostly negative for CD4, CD8, CD30, and CD56 (Figure 2). T-cell receptor gene rearrangements were positive for a clonal gamma T cell gene rearrangement.

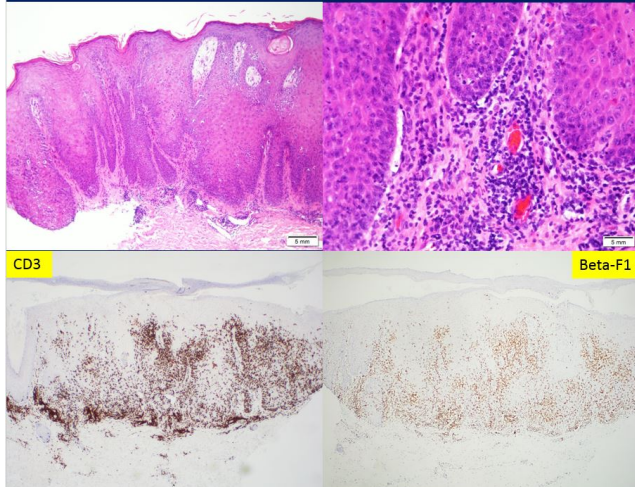
**Laboratory Data:** Whole blood flow cytometry showed a CD4/CD8 ratio of 4.5. A Leukemia/Lymphoma Panel showed no abnormality. Serum T-cell receptor gamma gene rearrangement was negative. A CBC showed a WBC of 11.8 (slightly elevated) and platelet count of 456. A CMP showed no abnormalities. HIV and RPR tests were negative. However, PET/CT showed innumerable FDG-avid cutaneous lesions although no FDG-avid lymph nodes.

**Clinical Course:** The patient was treated with Prednisone 60mg daily and then tapered off as there was no improvement after 3

**Figure 1**



**Figure 2**



weeks. Methotrexate was added at a dosage of 17.5mg weekly. The patient continues to develop new lesions with persistence of older lesions.

**Diagnosis:** CD4-/CD8- T-cell Lymphoproliferative Disorder (DDx: Probably Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T-cell Lymphoma which is CD8- in this case, with the possibility of an unusual Mycosis Fungoides)

**Points of Emphasis:** The histopathological features of skin with prominent epidermotropism of atypical lymphocytes

with clinically persistent plaques leads to a differential diagnoses that includes mycosis fungoides, primary cutaneous  $\gamma/\delta$  T-cell lymphoma and primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma. Often, these lesions can be differentiated by immunophenotyping with MF mostly showing a CD3+/CD4+/CD8-/BF-1+ phenotype, primary cutaneous  $\gamma/\delta$  T-cell lymphoma showing a CD3+/CD4-/CD8-/BF-1- phenotype, and primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma showing a CD3+/CD4-/CD8+/BF-1+ phenotype. However, all three of these entities can show CD3+/CD4-/CD8-

CD4/CD8 double-negative type MF has been commonly reported and has an indolent clinical course like that of typical MF.<sup>i</sup> Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma can be CD4-/CD8- in some cases.<sup>ii</sup> Finally,  $\gamma/\delta$  T-cell lymphoma is usually CD4-/CD8-, but shows negativity for BF-1.<sup>iii</sup>

Our case showed a CD4-/CD8-/BF-1+ immunophenotype which excludes the diagnosis of a  $\gamma/\delta$  T-cell lymphoma. However, the clinical course appears to be more aggressive due to the persistent plaques and multiple cutaneous FDG avid lesions. Therefore, an unusual CD8- primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma seems to be more likely than a CD4-/CD8- mycosis fungoides.

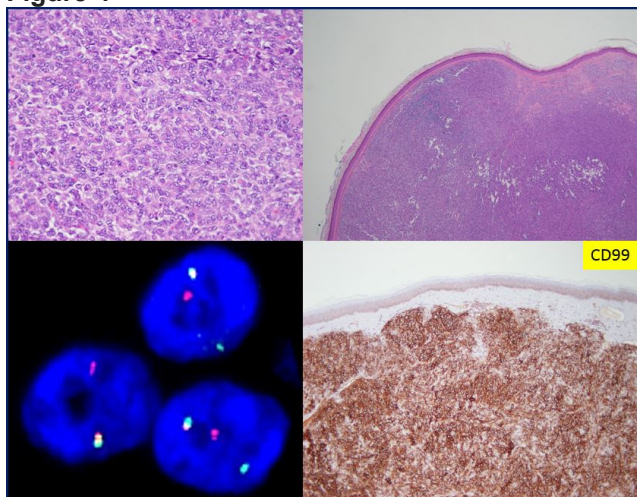
## CASE 2

**History:** A 75-year-old woman presented with a 1 cm erythematous nodule on the right anterior shoulder (Figure 3). The lesion had been present for an undetermined period of time.

**Figure 3**



**Figure 4**



**Physical Exam:** Involving the right anterior shoulder was a 1 cm, round pink to erythematous smooth firm nodule.

**Laboratory Data:** Non-contributory

**Histopathology:** A biopsy of the lesion revealed dermal sheets of small round blue cells with uniform round nuclei, scant cytoplasm, relatively minimal pleomorphism but with many mitotic figures. The tumor was diffusely and strongly positive for CD99, showed rare positivity for synaptophysin and was negative for EMA, Pan-CK, CD45, SOX-10, SMA, CK20, TTF-1, CD43, MUM-1, TdT,

CD34, and p40. Cytogenetic and molecular testing of the tumor was positive for rearrangement of the *EWSR1* (22q12) locus by FISH (Figure 4). An *EWSR1/FLI1* fusion transcript was detected by RT-DNA amplification respectively.

**Clinical Course:** The patient was found to have no evidence of systemic disease.

**Diagnosis:** Primary Cutaneous Ewing Sarcoma in an Adult

**Points of Emphasis:** Ewing sarcoma (ES) is a small round blue cell tumor that is closely related to the primitive neuroectodermal tumor (PNET) family. Ewing sarcoma is typically a neoplasm that occurs in bone or soft tissue of children and young adults. Rarely, it can present as a primary cutaneous neoplasm in adults.<sup>iv</sup> In this setting, the mean age is 22 years (range from 22 months to 77 years) with a nearly 2:1 female predominance. The median size of tumors reported was 2-3 cm most commonly on the extremities, followed by the head and trunk. Radiologic and clinical correlation is essential to confirm that the lesion is small and confined to the skin rather than a metastasis or direct extension from deep soft tissue or bone.

Histopathology typically reveals a nodular or sheet-like proliferation of undifferentiated small round blue cells. In this setting, there is a wide range of differential diagnoses when occurring in an adult including Merkel cell carcinoma, metastatic small cell carcinoma of the lung, lymphoma and small cell melanoma.<sup>v</sup> Ancillary studies can help further differentiate these entities. ES/PNET almost always characteristically show diffuse positivity for CD99 in a membranous pattern. Rarely, Merkel cell carcinomas and lymphoblastic lymphoma can express CD99



so that other stains may be required to distinguish these, however. ES/PNET may infrequently display focal positivity for pancytokeratin, S100, and neuroendocrine markers. Based on the varied immunohistochemical pattern of staining, there can be some diagnostic confusion between these entities, in which morphological and clinical correlation can aid in the diagnosis.

The characteristic chromosomal translocation in ES/PNET t(11;22)(q24; q12) resulting in the EWSR1-FLI1 fusion gene can greatly aid in the diagnosis. However, approximately 10% of ES/PNET have variant translocations. Rarely, the EWSR1 gene can be identified in other morphologically distinct entities as it has been described as a “promiscuous” gene.<sup>vi</sup>

Dual color break-apart EWS FISH probes can detect EWSR1 rearrangements regardless of the translocation variants. In this break-apart probe strategy, fluorosceinated probes normally flank the *EWSR1* gene. In the nucleus, abnormal (separate) red and green fluorochromes signify disruption of one copy of the *EWSR1* gene. In contrast, the normal allele is intact as evidenced by fused red and green signals indicating that the two probes are juxtaposed as a consequence of binding the same chromosomal locus.

Based on the relatively limited data in the literature on primary cutaneous Ewing sarcoma, it appears to have a much better prognosis than its skeletal or deep soft tissue counterpart. It has been established that the 10-year probability of survival was 91% with rare chance of metastatic disease.<sup>vii</sup> In light of the excellent prognosis of this tumor when confined to the skin, some authors have suggested that surgical excision should be

the primary mode of treatment with adjuvant therapy such as chemotherapy or radiotherapy playing a lesser role.

## CASE 3

**History:** A 73 year old male presented with a long standing lesion on the occipital scalp (Figure 5). A shave biopsy was submitted as “concerning for melanoma.”

**Physical Examination:** Irregular dark pigmented lesion on the scalp within an area of diffuse erythema extending onto the forehead.

**Laboratory Data:** Non-contributory

**Histopathology:** There was a dense diffuse infiltrate of spindle and epithelioid cells with pigment scattered throughout the lesion. Most of the neoplastic cells were closely opposed to one another and some were arranged in aggregations. There were a few dilated blood vessels but no irregular staghorn vessels with atypical cells in their lumina were noted (Figure 6). A diagnosis of malignant melanoma >2.1 mm was initially rendered.

The lesion was re-excised at which point features characteristic of angiosarcoma were identified with numerous, diffuse atypical irregular vessels with endothelial atypia seen throughout the dermis (Figure 7).

The submitting clinician was contacted and a request was made to review clinical photographs. Immunohistochemical stains were performed on the original biopsy and stains for ERG and CD31 were positive (Figure 8) while stains for Melan-A and SOX10 were negative. Of interest, one popular area originally sampled by shave

Figure 5



Figure 6

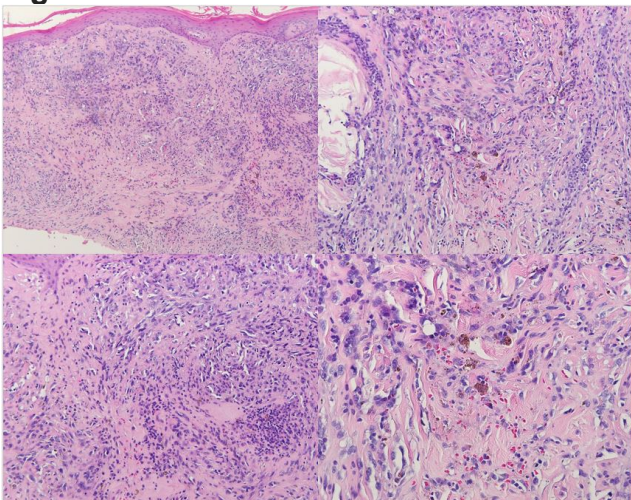


Figure 7

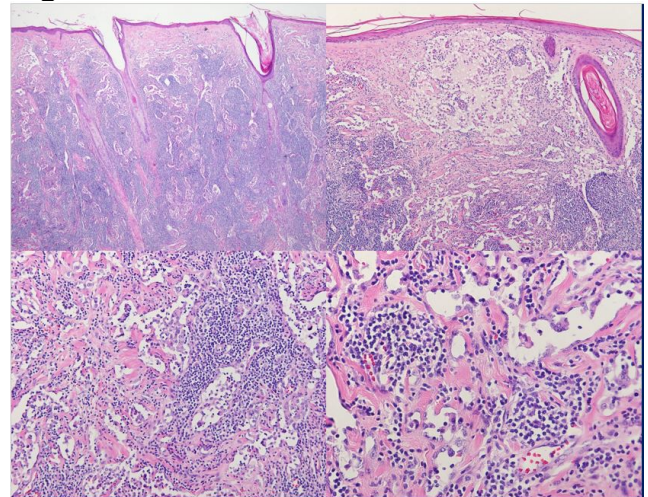
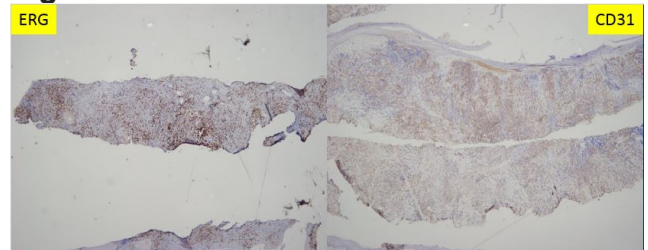


Figure 8



technique stained positively for S-100 protein.

**Diagnosis:** Pigmented Epithelioid Angiosarcoma Simulating Melanoma

**Clinical Course:** A re-excision was performed although there was diffuse involvement of lateral margins given the diffuse nature of the process. He was referred to radiation oncology for post-operative palliative radiotherapy.

**Points of Emphasis:** Angiosarcoma is an uncommon soft tissue neoplasm with a predilection for skin and superficial soft tissues. The epithelioid variant of angiosarcoma can sometimes be difficult to recognize and can mimic other neoplasms, usually epithelial lesions such as squamous cell carcinoma.<sup>viii</sup> In this case because the



lesion did not demonstrate significant vascular differentiation and had pigment which was probably hemosiderin, in the context of a clinical history of possible melanoma, the diagnosis of melanoma was made on the basis of morphology alone. It was only apparent on re-excision that the lesion truly represented angiosarcoma. Of interest in this case, there was positive staining for S-100 protein which may be seen in some angiosarcomas which can further complicate the diagnosis. Furthermore, the clinician noted only the pigmented papule and did not notice the larger, diffuse erythema which represented the more classic angiosarcoma.

It is important for clinicians to consider angiosarcoma in the differential diagnosis of cutaneous malignancies in lesions on the scalp of older individuals, especially if there are erythematous, macular “bruise-like” areas. Shave biopsies are often subject to sampling errors and malignancies such as angiosarcoma and other soft tissue neoplasms may demonstrate multiphasic patterns that may appear quite different within the same neoplasm. In this case, the biopsy sampled an epithelioid component that was not characteristic of angiosarcoma although it was recognizable as a malignancy. Unfortunately, the treatment of angiosarcoma is difficult as the lesion is diffuse and is not usually surgically resectable. Radiation therapy including brachytherapy may be useful for palliation although the prognosis remains extremely poor.<sup>ix</sup>

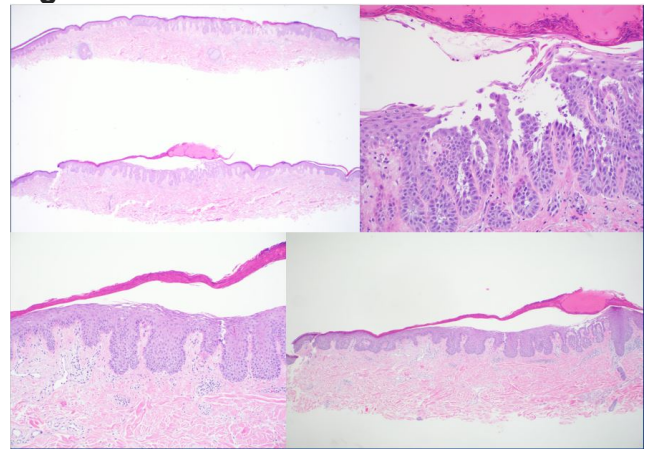
## CASE 4

**History:** A 58 year old Caucasian man presented to the dermatology clinic for

**Figure 9**



**Figure 10**



evaluation of a rash which had been present for about one year. He first noted redness and swelling in his legs, along with a scaly and pruritic eruption on the upper body. The rash generalized and involved most of the body. He had no history of asthma or atopy as a child (Figure 9). He was diagnosed with atopic dermatitis by a referring physician and was treated with dupilumab with no improvement.

**Physical Examination:** Nearly confluent, erythematous thin scaly plaques on the arms and legs, with erythematous scaly papules (some follicular) on the back and abdomen.

**Laboratory Data:** Noncontributory

**Histopathology:** Two biopsies were performed, both of which showed

psoriasiform epidermal hyperplasia irregular acanthosis and hyperkeratosis with small foci of spongiosis. Both biopsies also demonstrated foci of acantholysis, with some dyskeratosis as well (Figure 10).

**Clinical Course:** Patient was treated with triamcinolone ointment wet wraps and emollients, with some improvement. He will soon begin treatment with acitretin.

**Diagnosis:** Pityriasis rubra pilaris with acantholysis

**Points of Emphasis:** Pityriasis rubra pilaris is an uncommon papulosquamous eruption with several different clinical variants having been described.<sup>x</sup> The most common type (Type I) presents in adults with follicular-based, hyperkeratotic papules that spread inferiorly after starting on the upper body. Patients often develop palmoplantar keratoderma. An atypical presentation in the adult involves follicular hyperkeratotic papules, with an eczematous or ichthyosiform appearance to the plaques on the legs. These patients often have a more generalized distribution with chronic disease. The histological findings in pityriasis rubra pilaris vary by the acuity of the eruption and are most characteristic during the acute phase. Classic features include irregular acanthosis and a cornified layer with alternating orthokeratosis and parakeratosis. Follicular ostia are plugged with keratin, and inflammation is sparse. Foci of acantholysis, or acantholytic dyskeratosis, may be seen in approximately 20% of cases of pityriasis rubra pilaris.<sup>xi</sup>

In this case, the original clinical history did not include a differential diagnosis of psoriasis or PRP and the main histologic features identified were the acantholytic dyskeratosis which led to an initial diagnosis of Grover's

disease. When the patient was presented at a clinical conference, it became apparent that the psoriasiform dermatitis was the most important feature and a diagnosis of PRP with acantholysis was made. This emphasizes the importance of providing complete clinical information when submitting skin biopsies and in difficult cases, including clinical photographs or having the patient evaluated at a clinical conference as was done in this case can improve the accuracy of the diagnosis.

## CASE 5

**History:** A 79 year old Hispanic woman with a history of hypertension, diabetes, and renal insufficiency presented to the hospital with complaints of new onset melena and hematemesis. She was noted to have a one year history of a rash which started on her back and later spread to involve the arms, legs, and chest (Figure 11). She had some pruritus but no other symptoms, and she had not attempted any treatments other than cetirizine. She had a history of mild arthritis.

**Physical Examination:** There were pink dermal papules coalescing into plaques on the chest and back. Lichenified erythematous plaques were found on the elbows. Around the first and second fingers, there were periungual skin-colored to pink papules. There was also abnormality of the knees with swelling and joint dystrophy.

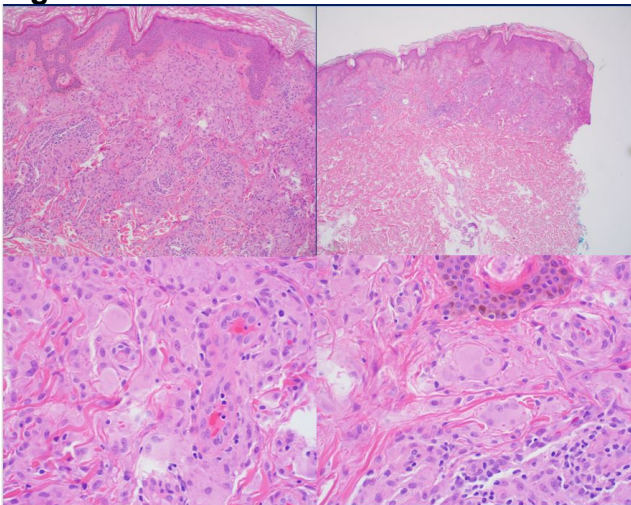
**Laboratory Data:** Significant anemia with a Hgb 6.3

**Histopathology:** A punch biopsy from a papule on the back revealed a dense dermal infiltrate of epithelioid histiocytes with amphophilic "ground glass" cytoplasm in a nodular configuration (Figure 12).

**Figure 11**



**Figure 12**



**Clinical Course:** The patient was admitted for an upper GI bleed, and an EGD revealed a ulcerated mass in the antrum of the stomach. A biopsy of this mass showed changes of chronic reactive gastropathy as may be seen near an ulcer, but no neoplasm was noted. Her bleeding stabilized with proton pump inhibitors. A repeat EGD is planned for the future, with probable re-biopsy of the antral mass.

**Diagnosis:** Multicentric reticulohistiocytosis

**Points of Emphasis:** Multicentric reticulohistiocytosis is a mucocutaneous papulo-nodular eruption formed by nodular accumulations of reticulohistiocytes in the

skin. When papules coalesce into plaques, a cobblestone appearance can be seen. The papules tend to predominate around joint spaces and classically present with a beaded appearance in a periungual distribution. Reticulohistiocytes are epithelioid histiocytes with abundant amphophilic cytoplasm having a ground-glass texture. Such histiocytes may be seen in isolated/solitary lesions (reticulohistiocytoma) or in diffuse eruptions (diffuse cutaneous reticulohistiocytosis). In the diffuse form, patients often develop a destructive arthropathy. Solid internal malignancies are found in association in approximately 20% of cases.<sup>xii,xiii</sup>

In this case, the diffuseness of the process was striking and given the extent of the process, many of the areas appeared more like a papulosquamous disorder rather than a widespread granulomatous process. While she had evidence of large joint involvement, she did not have the usual mutilating, destructive arthropathy that often involves smaller joints such as those of the hand.

## CASE 6

**History:** A 62-year-old woman with a history of hypertension was started on a new medication, Diltiazem ER, and developed a diffuse pruritic eruption 13 days later (Figure 13). Initially, the eruption was treated with an intramuscular injection of ceftriaxone and dexamethasone along with oral clindamycin, fluconazole, and oral hydroxyzine with topical mupirocin ointment.

**Physical Exam:** Involving the bilateral axillae, inguinal folds, trunk, and focally on the extremities are discrete and coalescing, focally round and targetoid erythematous to violaceous minimally scaling macules,



patches, and thin plaques. There were no associated systemic symptoms.

**Laboratory Data:** Non-contributory

**Histopathology:** Punch biopsies from the back revealed psoriasiform dermatitis with overlying parakeratosis and focal mounds of neutrophils in the stratum corneum. Involving the superficial dermis, there were a few scattered interstitial eosinophils, neutrophils, and extravasated red blood cells (Figure 14).

**Clinical Course:** The patient slowly improved after Diltiazem ER was discontinued.

**Diagnosis:** Urticarial drug reaction with psoriasiform features consistent with symmetric drug-related intertriginous and flexural exanthema.

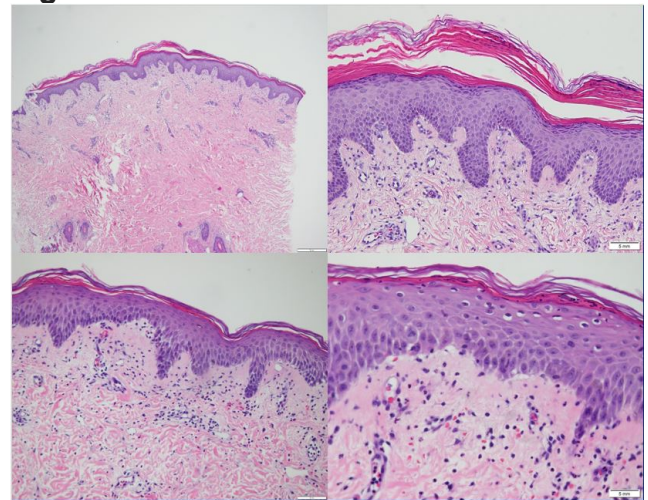
**Points of Emphasis:** Symmetric drug-related intertriginous and flexural exanthema (SDRIFE) is a form of systemic allergic dermatitis induced by a systemically administered drug. This eruption was previously called “baboon syndrome” as it commonly occurs on the buttocks as well as the intertriginous areas of the body. Beta-lactam antibiotics are the leading offending medication with case reports also including clarithromycin, doxycycline, metronidazole, infliximab, golimumab, and many more.<sup>xiv,xv,xvi,xvii</sup>

Clinically, the eruption is characterized by moderately ill-defined erythematous patches or thinly scaling plaques in intertriginous areas (axillae, groin, neck) as well as scattered on the trunk and extremities. Rarely, there may be pustulobullous lesions also. The eruption may develop within a few hours up to 2 weeks after the drug has been administered. The differential diagnosis

**Figure 13:**



**Figure 14:**



includes a morbilliform drug eruption, inverse psoriasis, intertrigo, atopic dermatitis, and acute generalized exanthematous pustulosis. The clinical history of a possible offending medication is necessary to making this diagnosis.

Histopathologically, SDRIFE has been described to show non-specific inflammatory findings including mild spongiosis, focal

vacuolar change, necrotic keratinocytes, a superficial perivascular lymphocytic infiltrate with interstitial dermal eosinophils and neutrophils.

It is thought that most of these reactions are a Type IV delayed hypersensitivity reaction mediated by cytotoxic T cells. In this interesting clinical case, the patient demonstrated the symmetric intertriginous eruption with focal areas resembling a fixed drug eruption clinically with mostly non-specific psoriasiform changes on histopathology.

Identifying and discontinuing the causative medication is imperative. Patch testing is possible but may have limited utility as there is limited absorption through the skin versus systemically and may not elicit a reaction. Controlled oral provocation testing has been thought to be useful in confirming the diagnosis. Along with discontinuation of the drug, oral anti-histamines and topical corticosteroids can be used.

## References:

The Zola Cooper- Lee T. Nesbitt Seminar highlights the importance of dermatologists correlating their clinical findings to that which

1. i Hodak E, David M, Maron L, Aviram A, Kaganovsky E, Feinmesser M. CD4/CD8 double-negative epidermotropic cutaneous T-cell lymphoma: an immunohistochemical variant of mycosis fungoides. *J Am Acad Dermatol* 2006; 55: 276-284.
2. ii Toshinari Miyauchi, Riichiro Abe, Yusuke Morita, et al. CD4/CD8 Double-negative T-cell Lymphoma: A Variant of Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T-cell Lymphoma? *Acta Dermato-Venereologica*. 2015;95(8):1024-1025.
3. iii Guitart J, Weisenburger DD, Subtil A, Kim E, Wood G, Duvic M, et al. Cutaneous gammadelta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. *Am J Surg Pathol* (2012) 36:1656-65.
4. iv Delaplace M, Lhommet C, de Pinieux G, Vergier B, de Muret A, Mchet L. Primary cutaneous Ewing sarcoma: a systematic review focused on treatment and outcome. *Br J Dermatol*. 2012 Apr;166(4):721-6.
5. v Machado I, Traves V, Cruz J, Llombart B, Navarro S, Llombart-Bosch A. Superficial small

## CONCLUSION

is seen under the microscope. Here we highlight 6 cases from this excellent seminar that demonstrate the significance of synthesizing both aspects for an appropriate diagnosis. This seminar is open to all dermatologists/dermatopathologists and benefits from cases that are submitted from all over. The upcoming conference will be held November 2, 2019 in New Orleans, Louisiana. All are invited to attend and share their knowledge and interesting cases.

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## Corresponding Author:

Etan Marks, DO  
Cockerell Dermatopathology  
Dallas, TX  
[cjcconsults@gmail.com](mailto:cjcconsults@gmail.com)

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- round-cell tumors with special reference to the Ewing's sarcoma family of tumors and the spectrum of differential diagnosis. *Semin Diagn Pathol.* 2013 Feb;30(1):85-94.
6. vi Boland JM, Folpe AL. Cutaneous neoplasms showing EWSR1 rearrangement. *Adv Anat Pathol.* 2013 Mar;20(2):75-85.
  7. vii Collier AB 3rd, Simpson L, Monteleone P. Cutaneous Ewing sarcoma: report of 2 cases and literature review of presentation, treatment, and outcome of 76 other reported cases. *J Pediatr Hematol Oncol.* 2011 Dec;33(8):631-4
  8. viii Prescott RJ, Banerjee SS, Eyden BP, Haboubi NY. Cutaneous epithelioid angiosarcoma: a clinicopathological study of four cases. *Histopathology* 1994;25 (5): 421-429.
  9. ix Bacchi CE, Silva TR, Zambrano E, et al. Epithelioid angiosarcoma of the skin. *Am J Surg Pathol* 2010;34:1334-43
  10. x Magro CM, Crowson AN. The clinical and histomorphological features of pityriasis rubra pilaris. A comparative analysis with psoriasis. *J Cutan Pathol* 1997;24:416-24.
  11. xi Avitan-Hersh E, Bergman R. The Incidence of Acantholysis in Pityriasis Rubra Pilaris- Histopathological Study Using Multiple-Step Sections and Clinicopathologic Correlations. *Am J Dermatopathol.* 2015 Oct;37:755-8.
  12. xii Kumar B, Singh N, Rahnama-Moghadam S, Wanat KA, Ijdo JW, Werth VP. Multicentric Reticulohistiocytosis: A Multicenter Case Series and Review of Literature. *J Clin Rheumatol* 2018;24:45-49.
  13. xiii Selmi C, Greenspan A, Huntley A, Gershwin ME. Multicentric reticulohistiocytosis: a critical review. *Curr Rheumatol Rep.* 2015;17:511.
  14. xiv Dogru M, Ozmen S, Ginis T, Duman H, Bostanci I. Symmetrical drug-related intertriginous and flexural exanthema (baboon syndrome) induced by amoxicillin-clavulanate. *Pediatr Dermatol.* 2012 Nov-Dec;29(6):770-1
  15. xv Nespoulous L, Matei I, Charissoux A, Bédane C, Assikar S. Symmetrical
  16. drug-related intertriginous and flexural exanthema (SDRIFE) associated with pristinamycin, secnidazole, and nefopam, with a review of the literature. *Contact Dermatitis.* 2018 Jul 30. doi: 10.1111/cod.13084
  17. xvi Labadie JG, Florek AG, Croitoru A, Liu W, Kronic AL. First case of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) due to Berberine, an over-the-counter herbal glycemic control agent. *Int J Dermatol.* 2018 Sep;57(9):e68-e70
  18. xvii Ozkaya E, Babuna G. A challenging case: Symmetrical drug related
  19. intertriginous and flexural exanthem, fixed drug eruption, or both? *Pediatr Dermatol.* 2011 Nov-Dec;28(6):711-4