

Benign Cutaneous Lymphoid Infiltrates

Introduction

The skin represents one of the organs in which the vast majority of diseases are associated with some manner of cutaneous lymphoid infiltration, or infiltration by other inflammatory cells. Just as benign processes can result in inflammatory disorders, so also atypical and malignant infiltrates of the skin can present a variety of different clinical manifestations. In addition to the classic inflammatory diseases of the skin such as psoriasis, seborrheic dermatitis, lichen planus, among others there is a definite group of diseases in which the presence of lymphocytic infiltrates occur with minimal epidermal involvement. These have been listed as the benign cutaneous lymphocytic infiltrates. They can be perivascular, nodular or diffuse in their presentation and some of them are so uniformly characteristic as they present that they are designated by specific names that allow not only for their diagnosis but often even for their causation. We will refer to a group of disorders, first which have classic names and very distinctive patterns of infiltration and then will discuss some of the more diffuse infiltrative lesions such as the so-called pseudolymphoma cutis or lymphocytoma cutis. For the sake of understanding and convenience of both clinical and pathologic manifestations, we will begin with a discussion of the superficial and then the superficial and deep cutaneous disorders and then the diffuse infiltrative lesions.

Superficial Cutaneous Lymphocytic Infiltration

Superficial Erythema Annulare Centrifugum

Superficial erythema annulare centrifugum is one of the first disorders to be designated as a gyrate or figurate erythema. This designation implies that there is an unusual pattern rather than a round lesion but one, which has some type of figurate appearance forming, for example, a C-shaped, or unusual S-shaped lesion or one with a highly irregular semilunar or serpiginous character. In erythema annulare centrifugum (EAC) there is a trailing scale behind the advancing edge of the lesion. These lesions occur at any age in life but are most common in early adulthood. The very initial lesions are small, pink, papule that eventually enlarges and forms an archiform pattern or semilunar pattern. The lesion can be present for days to months, or even rarely in some patients for years. The lesions do advance and can disappear and recur. The lesions may reach a diameter as great as 8 or 10 cm. There are different etiologic agents that result in EAC, approximately one-third of the lesions are associated with as an "id" reaction to superficial fungal infections at distant sites. In some patients the ingestion of bread molds will result in the presence of these lesions, they have also been described occasionally in association with drug reactions. Histopathology includes a prominent "sleeve-like" cuff of lymphocytes around superficial to mid-dermal vessels. In some cases there is a deep infiltrate. This type of so-called deep EAC is not associated with a scale but rather simply an irregularly shaped group of papules or plaque. The more superficial variant, that which is associated with the trailing scale characteristically affects the superficial vessels predominantly associated with mild exocytosis and

spongiosis with a prominent scale or scale crust. Sometimes one may see endothelial swelling and extravasation of red blood cells. The histology of the superficial infiltrate is more associated with activation of endothelial cells than the deeper infiltrate, in our experience. The differential diagnosis includes erythema chronicum in which one finds an infiltrate superficial and deep of lymphocytes admixed with plasma cells and often dissection of the vessel wall by the infiltrate as well a plasma cellular neuritis may be observed. The changes in the epidermis are minimal. The presence of positive serology for *Borrelia* in some cases. In other instances it is associated with tick bite reaction. Erythema marginatum can resemble the early phase of EAC that is associated with the neutrophil-rich urticatal type of reaction. Erythema gyratum repens, which can resemble both the superficial and deep infiltrate clinically has the distinctive picture, a so-called tree bark-like appearance to the skin caused by the infiltrate.

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Polymorphous Light Eruption

Polymorphous light eruption represents an idiopathic response to ultraviolet light. It combines features of a phototoxic reaction with those of a hypersensitivity reaction to ultraviolet light, which may be caused by either UVA, UVB or both wavelengths in some patients. The lesions present as papules or plaques in a light exposed area. They are erythematous and are sometimes associated with itching. Characteristically the history is appearance of these lesions 30 to 45 minutes to several days after exposure to either sun or ultraviolet light. Resolution in one to two weeks is common. The lesions are present usually on the sun-exposed areas of the body that after recurrences of the eruption, they may extend to non-sun-exposed areas as well. Because these lesions are commonly in a light exposed area they raise often the diagnosis of lupus erythematosus and one study has shown that approximately half of lupus patients had symptoms consistent with polymorphous light eruption sometimes for years before they developed the autoimmune disease. Histopathologically there are a group of changes that allow for correct diagnosis. First, in the epidermis there may be focal parakeratosis, spongiosis occurs to a mild degree in many cases but in some there is spongiotic vesiculation. Dyskeratotic cells or apoptotic cells are scattered in the epidermis of the effected skin. There is vasculopathy of the dermal/epidermal junction in most cases. Approximately 50-60% of the plaque like light eruptions show vacuolopathy resembling the vacuolopathy of the lupus erythematosus. There is no thickening of the basement membrane zone and no epidermal atrophy. While papillary dermal edema of marked degree is characteristic. Some cases, in fact do not show marked edema of the papillary dermis but rather a more diffuse edema of the papillary reticular dermis. Characteristically, the infiltrate on low power shows a gradual tapering with a predominance of lymphocytes above tapering to lymphocytes of very few in number even around vessels as deep as subcutaneous fat. Superficial vessels show characteristically vacuolization of the endothelial cells and the

endothelial basement membrane zone they are associated not only with a perivascular lymphocytic infiltrate but also an edematous perivascular change that gives one the impression that the cells are present in an edematous background. Rare neutrophilic debris is present as well as rare extravasation of red blood cells superficially. The changes of endothelial vacuolization and activation are most superficial that do not affect the deeper dermis. Focal blood and mucin may be observed in some reactions. Direct immunofluorescence examination will show focal IgM and C3 deposition in some blood vessels with occasional IgM at the dermal/epidermal junction of very weak intensity. The differential diagnosis includes phototoxic reactions. Phototoxic reactions usually show extensive apoptosis and dyskeratosis. There is a neutrophilic infiltrate at the dermal/epidermal junction with so the same degree that is associated with the extensive dermal/epidermal necrosis. A mild perivascular lymphocytic infiltrate may be present superficially but the overwhelming changes are those of the epidermal change. Photoallergic reactions are very similar to contact dermatitis. The presence of occasional dyskeratotic cells and endometrial cell changes which occur also in this type of reaction are distinguishing features are the occasional neutrophilic debris. Also, the reactions of contact dermatitis have intense very closely applied lymphocytes without the edema of the perivascular adventitia that is seen in association with the polymorphous light eruption. The reactions of lupus erythematosus can be distinguished on the following basis. First in acute lupus erythematosus there is massive mucinosis and debris along the dermal/epidermal junction with attenuation of the epidermis. In the more chronic lesions there is base membrane zone thickening with atrophy of the epidermis.

Chronic Photo Dermatitis

Chronic photo dermatitis also known as actinic reticuloid is associated with a very prominent perivascular lymphoid infiltrate with a mixture of histiocytes. The cells in perivascular array show activation of the lymphocytes and are associated with obvious cytoplasmic in cells with immunoblastic-like changes. There is fibrosis of the papillary dermis with hyperkeratosis and usually increased granular cell layer. In the papillary dermis there are very activated appearing histiocytes with almost dendritic-like forms with the dendrites frequently arrayed pointing in a direction perpendicular to the long axis of the epidermis.

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Jessner's Lymphocytic Infiltrate of the Skin

Jessner's lymphocytic infiltrate presents either as group papules or a plaque or plaques that are usually confined to sun exposed area, predominantly on the head and neck and upper trunk. Most patients with this disorder are in the age range of adult life from 30 to 60 years of age, however, it may be observed in childhood, and even later in life. The lesions of Jessner's lymphocytic infiltrate usually are pink papules or plaques, often non-symptomatic that is with no pruritus or other sensations. The lesions do tend to resolve. There is an overlap between this entity and the so-called non-scarring discoid lupus erythematosus. In patients with these reactions there is no evidence of collagen vascular disease. Direct immunofluorescence of these lesions fails to reveal changes other than occasional IgM or C3 scattered with weak intensity in perivascular array. Histopathologically there is a quite extensive superficial and deep perivascular and periadnexal infiltrate of fully formed mature lymphocytes. In some cases there is even extension into the subcutaneous fat. Eosinophils may be observed in the infiltrate. The infiltrate characteristically tapers as the lesion infiltrates the dermis. There is no evidence of interface dermatitis at the epidermal junction or along follicles, which helps to differentiate this lesion from variants of lupus erythematosus. Although there may be focal infiltrate of the external root sheath, there is no destruction of the external root sheath. Focal mucinosis occurs in approximately 40% of cases. The changes are associated predominantly with a T cell infiltrate. In some of the lesions with a more dense inflammation one may observe foci of B cell infiltration. In other lesions, one can observe CD68 positive cells admixed with lymphocytes around the vessels. The lupus band test is negative. One feature of Jessner's lymphocytic infiltrate that is helpful to distinguish it from lupus is that there are occasionally B cells admixed as indicated above. This presence of B cells rules out the diagnosis of lupus erythematosus virtually exclusively. The differential diagnosis includes non-scarring DLE. In lupus erythematosus there is definitely interface dermatitis yet there may be more dermal mucinosis. It is interesting that both disorders do respond, that is Jessner's and non-scarring DLE to antimalarials. Jessner's infiltrate can be distinguished from polymorphous light eruption by the presence of marked edema in the papillary dermis, by the presence of spongiosis in the epidermis and also by the presence of occasional eosinophils admixed with the infiltrate in polymorphous light eruption.

Non-Scarring Discoid Lupus Erythematosus/TUMID Lupus Erythematosus

Clinical

This group of patients presents with quite prominent plaques in photosensitized areas of the skin, especially head and neck, anterior chest, and the upper back. These lesions wax and wane and will respond both to Plaquenil systemically and intralesional injections to steroids. The patients have negative serologies. The band test may show focal staining with IgM and C3 at the dermal/epidermal junction. This lesion is considered to be a variant of discoid lupus erythematosus. Histopathologically, the most important differential diagnosis of this lesion is Jessner's lymphocytic infiltrate. The angiocentric and periadnexal infiltrate of Jessner's is associated with mucinosis but in non-scarring discoid erythematosus there is interface dermatitis predominately of the intrafollicular epidermis and of the follicular epidermis. These changes are associated with degenerative epithelial changes. There is no evidence of abnormal serologies nor do the patients have evidence of C5B9 or IgG at the dermal/epidermal junction.

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Deep Gyrate Erythemas

The deep gyrate erythemas represent a group of lesions that are associated with very dense lymphoid infiltrate in perivascular and periappendiceal array with no evidence of activation of the endothelial cells in the classic deep gyrate erythema that is a lymphocytic infiltrate. The group of disorders also includes erythema chronic migrans, erythema gyratum repens as well as erythema marginatum as a peculiar neutrophil mediated lesion.

Erythema chronica migrans

This disorder is a hallmark cutaneous manifestation of LYME disease. It presents as a lesion around a bite site that migrates gradually and forms rings clinically. It is a very characteristic lesion. Histologically the lesion shows a prominent perivascular lympho-eosinophilic infiltrate but with admixed plasma cells. The characteristic features include prominent endothelial cell activation with swelling as well as the infiltration of the lymphoid cell and plasma cells into the vessels of both the small veins, the medium size veins dissecting apart the area with edema. There can be focal mucin deposition. There is a plasma cell neuritis.

Erythema gyratum repens

Erythema gyratum repens is a rare manifestation of a neoplastic disease, usually carcinoma of the lung but it has also been associated with other malignancies with tuberculosis with pityriasis rubra pilaris in a few patients and rarely with the CREST syndrome. The lesion is represented by broad irregularly shaped patches that resemble the bark of a tree as they are separated by clear skin. What is so fascinating in this disorder is that it may be associated with carcinoma of the lung, and on extirpation of the tumor, the lesions of erythema gyratum repens will disappear but then recur if the malignancy recurs. In the histopathology, this shows usually a prominent perivascular lymphoid infiltrate with variable edema and admixed eosinophils superficial and deep. In some instances it presents as a diffuse lympho-eosinophilic infiltration of the dermis admixed with histiocytes. Clinical correlation is extremely important in this disorder.

Erythema marginatum

Erythema marginatum is a disorder that is associated with rheumatic fever and it may be associated with rheumatoid carditis. However, it also occurs spontaneous and may be associated with strept infection. The lesions clinically are small, round, semilunar shaped lesions or irregular shaped papules and plaques that are very evident and occurring rapidly and resolving with sometimes 30 to 50 minutes. They typically involve the trunk. In the histopathology, there is a prominent vascular lymphoid infiltrate but most strikingly there are numerous neutrophils in perivascular and intervascular array with debris. The neutrophilic debris is scattered throughout the entire dermis and thus differs from other types of lesions that would be associated with vasculitis, for example. There is no evidence of fibrinoid necrosis nor is there any evidence of extravasation of red blood cells but simply neutrophils with debris. Occasionally the epidermis will show a dyskeratotic cell and there may be intraepithelial neutrophils. The main differential diagnosis of this lesion is leukocytoclastic vasculitis but there is minimal or no fibrin distribution in this lesion as one finds in urticarial vasculitis also there is not the diffuse debris but rather a rare neutrophil scattered through the dermis and to some debris around the vessels with or without fibrinoid necrosis.

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Cutaneous B-cell Pseudolymphoma (Lymphocytoma Cutis, Benign Cutaneous lymphoid Hyperplasia)

Introduction

With the appearance of an appreciation of a marginal zone lymphoma and follicular lymphoma in the skin, the entity of cutaneous B cell lymphoma has assumed a greater importance in diagnosis because of the fact that it is not a lymphoma but in some instances with recurrence can lead to lymphoma. As noted, by Philip McKee, the realization that germinal center formation does not mean necessarily a benign reactive process has changed our approach to these lesions and we must be extremely careful in diagnosis of the pseudolymphomatous lesion.

Clinical features

A prominent erythematous to plum colored nodule or plaque is characteristic of this lesion. The pseudolymphomatous areas occur in the same sites often as the well-differentiated B cell lymphoma such as marginal zone lymphoma. The most common sites are face, head and neck, chest and upper extremities. The lesions are usually singular but in some patients they can be multiple. Women are more affected than men and mostly patients are under 40 years of age. The Borrelia associated pseudolymphoma that is more common in Europe than in the United States, affects the areas of the head but also the nipple of the areola and the scrotum. These lesions are more commonly noted in children. It is interesting that when lymphocytoma cutis is present on the trunk, it is associated with multiple lesions often. Histopathologically, the lesion has been described to show a so-called top-heavy infiltrate. However, indeed, it can be seen as a diffuse infiltrate or it can be bottom heavy as well that is affecting the subcutaneous fat predominantly. Lymphoid follicles with germinal centers are usually present and they often have a clear-cut mantle zone. Tissue body macrophages are common and the germinal center shows the zonation that is characteristic of the germinal center in lymph nodes. The interfollicular population includes lymphocytes, plasma cells, histiocytes and eosinophils. Occasionally multinucleate giant cells are present and even often granulomatous elements. Blood vessels are associated with very prominent endothelial cell hypertrophy and swelling in some instances. Immunohistochemically these lesions are composed of B cells and T cells but the latter usually are equal to the B cells or can predominate. The germinal centers can be highlighted with CD21. There are polyclonal light chains, evidence of polyclonality in light chain examination for kappa and lambda. One very important differential diagnostic feature that we have found to be very useful is that the hair follicles can be infiltrated by B cells in lymphoma whereas this infiltration does not occur in for example, marginal zone lymphoma, whereas this infiltration does not occur in B cell lymphoma. The B cells may be CD21 positive or CD19 positive. The pathogenesis of this lesion is very interesting in that these lesions can occur as a result,

for example, repeated contact dermatitis. Therefore, these lesions are clonal for T cells. They can also follow tattooing, vaccination, repeated arthropod reactions, or even a hyposensitization to injection of antigen for hyposensitization. Indeed, in Europe, and also less so in the United States, these lesions have been shown to be associated with *Borrelia-burgdorferi* infection. In Europe they have reported that lesions of pseudolymphoma caused by *Borrelia* can give rise to cutaneous B cell lymphoma. This finding has been very rare in the United States.

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