REVIEW

Approaches to the Dermatopathologic Diagnosis of Figurate Lesions

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Manuscript received September 28, 2010; accepted for publication December 26, 2010

KEYWORDS
Figurate erythema; Annular erythema; Dermatopathology

Abstract Both clinical and pathologic findings must be considered when diagnosing figurate skin lesions, which are often seen in routine practice. Although a skin biopsy may sometimes be diagnostic, more often the information provided is nonspecific. In an attempt to offer an approach to diagnosing these dermatoses, we have classified annular lesions according to the presence of lymphocytic, neutrophilic-eosinophilic, or granulomatous infiltrates, and infiltrates containing plasma cells. Neoplastic annular lesions are included in a separate group. Lesions containing lymphocytic infiltrates include superficial and deep erythema annulare centrifugum and the differential diagnosis includes a large number of conditions. In the neutrophilic-eosinophilic class, we include annular psoriasis, vasculitis, linear immunoglobulin A dermatosis, eosinophilic dermatitis, erythema marginatum rheumatica, and annular erythema of infancy. Sarcoidosis and granuloma annulare are the prototypical annular lesions containing granulomas. Secondary syphilis is typical of lesions containing plasma cells. Mycosis fungoides is the principal skin tumor that may initially manifest with annular lesions.

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PALABRAS CLAVE
Eritemas figurados; Eritema anular; Dermatopatología

Aproximación al diagnóstico dermatopatológico de las lesiones figuradas

Resumen Las lesiones cutáneas figuradas son muy frecuentes en la práctica diaria, y en la mayoría de las ocasiones requieren una adecuada correlación clínico-patológica para llegar a un diagnóstico correcto. En algunos casos la biopsia mostrará hallazgos específicos que permitirán hacer el diagnóstico, pero en la mayor parte de ellos los datos serán inespecíficos. En un intento de aproximarnos al diagnóstico de estas dermatosis hemos clasificado las lesiones anulares según el tipo de infiltrado inflamatorio: linfocitario, neutrofílico-eosinofílico, granulomatoso y con células plasmáticas; y hemos incluido un

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Introduction

Figurate erythemas are skin eruptions of migrating or fixed lesions that trace annular, circinate, arciform, concentric, or polycyclic patterns. Dermatopathologic examination of such lesions potentially reveals well-defined features that orient diagnosis, as in the case of granuloma annulare, annular psoriasis, or subacute annular lupus erythematosus. In ringworm, the most common cause of annular lesions in both adults and children, biopsy is not needed for diagnosis in most cases. For other conditions, histologic findings are nonspecific and often subtle, making it difficult for the pathologist to suggest a diagnosis when examining the material sampled. This is the situation for the conditions we call figurate erythemas, particularly erythema annulare centrifugum (EAC), chronic erythema migrans, and erythema gyratum repens.

Taking a practical approach in the interest of furthering histologic diagnosis, we have grouped the various diagnostic entities that present with figurate erythemas according to the inflammatory infiltrate that can be observed in the biopsy specimen (Table 1).

Lymphocytic Figurate Erythemas

EAC, the prototypical figurate erythema, is an inflammatory skin disease of uncertain etiology that begins as a maculopapular rash that spreads centrifugally as the center clears. Lesions tend to converge, creating arciform or polycyclic configurations. The term EAC is conceptually controversial, as many authors consider it to be a hypersensitivity reaction that can be triggered by various processes or agents (infections, drugs, tumors, and several systemic diseases) rather than a specific diagnostic category.

EAC was first described in 1916 by Darier as a self-limited, recurring annular eruption that is characterized by a normal epidermis and the presence of a perivascular lymphocytic inflammatory infiltrate that may be superficial or extend deep into the dermis. Two clinical variants were later proposed: one is the deep form introduced by Darier and the other is superficial. Ackerman stressed the importance of distinguishing the 2 types in 1978, and in 1997 he concluded with colleagues that the superficial form (which he termed EAC or superficial figurate erythema) was unrelated to the deep form, which he preferred to call erythema figuratum. Most dermatopathology textbooks, however, have continued to consider these EAC variants to be subtypes of the same process and to have distinct histologic characteristics. McKee and colleagues assert that depth of infiltration and the presence of epidermal lesions are unrelated findings, whereas Weedon and Barnhill note that unlike deep lesions, those with superficial infiltrates are associated with spongiosis and crust formation. In the largest case series (73 patients), published in 2003, Weyers and colleagues concluded, on the basis of both clinical and histologic features, that superficial and deep EAC were different diagnostic entities. Scaling is the main distinguishing clinical sign of superficial EAC. Histology, in addition to confirming the depth of the inflammatory infiltrate, makes evident other differences between the superficial and deep forms (Table 2), particularly concerning the presence of epidermal involvement (Figures 1-3). While isolated erythrocytes, eosinophils, and neutrophils can be found in the dermis in both types of EAC, plasma cells are absent.

When lesions that share an etiologic factor are classified on the basis of histologic findings, the diagnosis is usually superficial EAC, as the deep form is rare. In keeping with...
the positions reviewed above, superficial EAC is currently considered to be a distinct clinical-pathologic entity whose course is chronic and recurring whereas deep EAC seems to be an annular variant of other skin diseases, particularly of lupus erythematosus tumidus, although polymorphous light eruption, chronic erythema migrans, indeterminate leprosy, erythema gyratum repens, necrolytic erythema erythrodermatoma variabilis, and mycosis fungoides should all be considered as differential diagnoses (Table 3). If a specific diagnosis cannot be made, a proposal is to call the lesions deep figurate erythemas.

The differential diagnosis of superficial EAC should include other types of superficial spongiotic dermatitis (Table 3): allergic contact dermatitis, nummular eczema, pemphigus, eczema herpeticum, subacute lupus erythematosus, subacute cutaneous lupus erythematosus, discoid lupus erythematosus, bullous pemphigoid, linear IgA dermatosis, bullous pemphigoid, pemphigus, pemphigus vulgaris, pemphigus foliaceus, and pemphigus erythematosus.

Table 1  Figurate Lesions: Classification According to the Principal Component of the Inflammatory Infiltrate

<table>
<thead>
<tr>
<th>Lymphocytic</th>
<th>Neutrophilic-Eosinophilic</th>
<th>Granulomatous</th>
<th>Plasma Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAC, superficial form</td>
<td>Annular psoriasis</td>
<td>Granuloma annulare</td>
<td>Secondary syphilis</td>
</tr>
<tr>
<td>EAC, deep form</td>
<td>Sneddon-Wilkinson syndrome</td>
<td>Sarcoïdosis</td>
<td></td>
</tr>
<tr>
<td>Polymorphous</td>
<td>IgA pemphigus</td>
<td>Borderline leprosy</td>
<td></td>
</tr>
<tr>
<td>light eruption</td>
<td>Linear IgA dermatosis</td>
<td>Tuberculoid leprosy</td>
<td></td>
</tr>
<tr>
<td>Lupus erythematosus tumidus</td>
<td>Bullous pemphigoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute lupus erythematosus</td>
<td>Leukocytoclastic vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic erythema migrans</td>
<td>Eosinophilic vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminate leprosy</td>
<td>Urticarial vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema gyratum repens</td>
<td>Eosinophilic dermatosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrolytic erythema</td>
<td>Erythema marginatum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>rheumatica</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrokeratodermia variabilis</td>
<td>Annular erythema of infancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Eosinophilic erythema</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EAC, erythema annulare centrifugum; IgA, immunoglobulin A.

Table 2  Erythema Annulare Centrifugum: Clinical-Pathologic Variants

<table>
<thead>
<tr>
<th>Histologic Findings</th>
<th>EAC, Superficial Form</th>
<th>EAC, Deep Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis</td>
<td>On occasion</td>
<td>No</td>
</tr>
<tr>
<td>Spongiosis</td>
<td>Focal</td>
<td>No</td>
</tr>
<tr>
<td>Parakeratosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dyskeratosis</td>
<td>No</td>
<td>On occasion</td>
</tr>
<tr>
<td>Lesion at the dermal-epidermal junction</td>
<td>No</td>
<td>Focal in &lt;50% of cases</td>
</tr>
<tr>
<td>Inflammatory infiltrate</td>
<td>Superficial</td>
<td>Superficial-to-deep</td>
</tr>
<tr>
<td>Dermal edema</td>
<td>On occasion</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviation: EAC, erythema annulare centrifugum.

Table 3  Figurate Lesions With a Lymphoid Infiltrate: Differential Diagnosis

<table>
<thead>
<tr>
<th>Diagnostic Entity</th>
<th>Differential Diagnosis</th>
<th>Key Histologic Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAC, superficial form</td>
<td>Spongiotic dermatitis, Allergic contact dermatitis, Nummular eczema, Pityriasis rosea, Polymorphous light eruption, Lupus erythematosus tumidus, Subacute lupus erythematosus</td>
<td>Spongiotic pattern, Focal (superficial EAC), Diffuse (spongiotic dermatitis)</td>
</tr>
<tr>
<td>EAC, deep form</td>
<td>Chronic erythema migrans, Indeterminate leprosy</td>
<td>Dermal edema, Dermal mucin, Epidermal atrophy, Periappendiceal inflammation, Mucin, Eosinophils and plasma cells, Perineural inflammation</td>
</tr>
</tbody>
</table>

Abbreviation: EAC, erythema annulare centrifugum.
and pityriasis rosea. Microscopy in pityriasis rosea is nonspecific but its clinical presentation is characteristic. A viral etiology has been suggested, as polymerase chain reaction amplification has demonstrated the presence of herpes virus 6 and 7 DNA in lesions. Diffuse spongiosis, as opposed to the focal spongiosis of superficial EAC, will be a more typical finding in allergic contact dermatitis and nummular eczema, but histologic and clinical signs should be correlated for diagnosis. These 2 conditions do not usually manifest as figurate erythemas, although rare cases have been reported. Differential diagnosis should include erythema multiforme, which typically forms target lesions. The histologic profile, in addition to a perivascular inflammatory infiltrate that may also contain eosinophils, is noteworthy for the presence of necrotic keratinocytes (isolated or in groups) throughout the epidermis and for the formation of a vacuole at the dermal-epidermal junction.

Polymorphous light eruption, which is the most common of light-induced skin diseases, is characterized by a papular, erythematous rash, vesicles or plaques that appear after exposure to ultraviolet light. In addition to a superficial-to-deep mononuclear infiltrate forming around vessels, the histologic profile includes edema within the papillary dermis (a finding with high value for differential diagnosis), acanthosis, spongiosis, dyskeratosis, exocytosis; a periadnexal infiltrate with eosinophils and neutrophils may occasionally be present (Figure 4).

Lupus erythematosus tumidus is a cutaneous lupus subtype that constitutes a separate entity. It is characterized by erythematous plaques that may be annular or gyrate and are found on skin exposed to sunlight. Histology shows a mononuclear inflammatory infiltrate, which may be periadnexal, and abundant dermal mucin deposits. Epidermal changes in lupus erythematosus tumidus (follicular plugs, vacuolar degeneration at the dermal-epidermal junction, and thickening of the epidermal basement membrane) are minimal and immunofluorescence is negative. Histologic examination of subacute annular lupus erythematosus and neonatal lupus erythematosus reveal the usual features of lupus, offering no distinctive findings.

Chronic erythema migrans appears in the first stage of Lyme disease (systemic infection by *Borrelia burgdorferi*). The characteristic annular lesion appears between the third and 30th day, arising from a papule caused by a bite from a tick, the vector for the spirochete. The papule spreads outward, reaching 30 to 50 cm in diameter. The initial histologic observations reflect the insect bite (a polymorphic infiltrate that may show epidermal necrosis) and an annular plaque with a superficial and deep perivascular lymphocytic inflammatory infiltrate, in which plasma cells and eosinophils can often be observed (Figure 6). Spirochetes can be identified with silver stains in 40% of cases.

Indeterminate leprosy occasionally presents with annular lesions and histologic findings that resemble those of deep EAC, with a lymphocytic infiltrate and without granulomas or foam cells. The lack of histologic specificity makes
for a difficult diagnosis in geographic areas where the disease is not endemic. The observation of a perineural inflammatory infiltrate in a biopsy specimen (Figure 7) should lead to suspicion of this disease. Immunostaining for S100 protein is advisable to help identify small nerve structures.

Figure 5  A, Lupus erythematosus tumidus (hematoxylin-eosin, original magnification, ×100). B, Abundant mucin deposition (Alcian blue; original magnification, ×200).

Figure 6  A, Chronic erythema migrans (hematoxylin-eosin; original magnification ×100). B, Scant chronic lymphocytic inflammatory infiltrate with eosinophils and plasma cells (hematoxylin-eosin; original magnification, ×400).

Erythema gyratum repens takes the form of concentric erythematous bands on the skin. This peculiar presentation usually indicates the diagnosis in most cases, although this pattern has also been seen in lupus erythematosus and urticarial vasculitis. Erythema gyratum repens is sometimes associated with carcinomas in a variety of organs (lung, esophagus, stomach, kidney, breast, and uterus). Histology usually demonstrates hyperkeratosis, parakeratosis, acanthosis, spongiosis, and a superficial perivascular lymphocytic infiltrate.

Necrolytic migratory erythema, along with glossitis, stomatitis, glucose intolerance, and anemia, is a component of the so-called glucagonoma syndrome. This syndrome, described in pancreatic glucagonoma,
has also been linked to adenocarcinomas of the jejunum, insulinoma, advanced cirrhosis, and hyperglucagonemia not associated with a tumor. Cutaneous lesions on the trunk, axillas, perineum, thighs, buttocks, and other locations resemble annular erythema or toxic epidermal necrolysis. The pathogenesis of these erythemas is uncertain, although the catabolic effects of excess glucagon secretion are believed to be involved, given that the histologic findings are similar to those of nutritional deficiency diseases (pellagra, enteropathic acrodermatitis) and that the rash disappears after intravenous administration of amino acids. Histologic findings depend on when the lesion is biopsied in the course of disease, but there is usually a lymphocytic infiltrate in the papillary dermis; polymorphonuclear neutrophils may be present. The most salient observation is the presence of pale, vacuolated keratinocytes in the highest layers of the epidermis. These keratinocytes can become necrotic, and subcorneal or intraepidermal clefts may appear, sometimes with a neutrophilic inflammatory content, forming pustules (Figure 8).

Finally, other diseases can cause figurate erythemas but show scant perivascular lymphocytic infiltrate in biopsy specimens. One such entity is erythrokeratoderma variabilis, an autosomal dominant disorder of keratinization in which orthohyperkeratosis, acanthosis with a prominent granular layer, and papillomatosis can be observed in addition to the inflammatory infiltrate.

**Figurate Erythemas With Neutrophils and Eosinophils**

The group of figurate erythemas with neutrophils and eosinophils include psoriasis, certain bullous skin disorders, vasculitis, eosinophilic dermatitis, and erythema marginatum of rheumatic fever.

Annular psoriasis may be a form of pustular psoriasis, particularly if it develops in infancy. Histologic findings in such cases differ little from those typically found in psoriasis (Figure 9). Microabscesses are nearly always present in the stratum corneum and spongiform pustules can often be observed. Exocytosis of neutrophils and psoriasiform acanthosis are usually not very evident. Periodic acid-Schiff staining is recommended to rule out fungal infection. Subcorneal pustules, neutrophils in the epidermis, and a superficial and deep perivascular lymphocytic infiltrate can be observed in Sneddon-Wilkinson syndrome (subcorneal pustular dermatosis). Immunoglobulin A (IgA) pemphigus should be ruled out by immunofluorescence in such cases.

Clinical lesions resembling those of erythema annulare centrifugum have been reported for linear IgA dermatosis on rare occasions. The inflammatory infiltrate contains neutrophils, and papillary microabscesses occasionally form; eosinophils can also be observed (Figure 10). Given that rare cases of bullous pemphigoid and pemphigus vulgaris presenting with figurate erythemas have also been reported, these conditions should be considered.

Annular leukocytoclastic vasculitis, of which only 17 cases have been reported, is a rare type of vasculitis. This condition has been found in association with systemic diseases (such as...
sarcoidosis, ulcerative colitis, cryoglobulinemia in hepatitis B, Sjögren syndrome, and neoplastic diseases), in pregnancy, and in patients taking such drugs as sorafenib (a tyrosine kinase inhibitor used to treat renal cell carcinoma) or amlodipine (a calcium channel blocker). The histologic profile is of a leukocytoclastic vasculitis of the small vessels with a mixed neutrophilic and eosinophilic inflammatory infiltrate. The condition known as recurrent cutaneous necrotizing eosinophilic vasculitis, described by Chen and coworkers, can also present with annular erythema. Histologic examination shows a necrotizing vasculitis of small dermal vessels with an infiltrate that is almost entirely eosinophilic, without leukocytoclasis (Figure 11).

Acute annular urticaria (urticaria multiforme) is known to occur in infancy as a histamine-mediated hypersensitivity reaction following viral or bacterial infections or after the use of a medication. While diagnosis is mainly clinical, the histologic profile is known to coincide with that of common urticarial rashes; that is, examination shows interstitial and perivascular edema with vascular dilation and a scant mixed inflammatory infiltrate.

Eosinophilic dermatitis, a rare form of hypereosinophilic syndrome, is characterized by skin lesions (papules, nodules, and/or erythematous macules) and peripheral blood eosinophilia (>20%) without evidence of other systemic involvement. Miljkovic et al described a man with a history of chronic lymphoid leukemia in remission associated with eosinophilic dermatitis and erythema annulare centrifugum. In that case histology showed an abundant superficial and deep perivascular and interstitial eosinophilic infiltrate.

Erythema marginatum rheumatica is an annular or polycyclic eruption included in the clinical picture of 1% to 18% of cases of rheumatic fever. The rash is usually found on the trunk and proximal surfaces of the extremities. Histology shows a perivascular neutrophilic infiltrate with leukocytoclasis and no evidence of vasculitis with fibrinoid necrosis.

In addition to the annular erythema mentioned above, various annular erythemas that are usually self-limited can appear in infancy. Histologic examination of the lesions shows an eosinophilic or neutrophilic infiltrate. Annular erythema of infancy is a rare condition in which annular or circinate erythematous lesions develop before the age of 1 year. Histology reveals a lymphocytic inflammatory infiltrate with eosinophils. A variant, called eosinophilic annular erythema is characterized by a diffuse dermal infiltration of abundant eosinophils with some lymphocytes. Dermal mucin deposition and vacuole formation at the dermal-epidermal junction have sometimes been reported; in the absence of flame figures or eosinophil degranulation, such findings allow Wells syndrome to be ruled out. Finally, neutrophilic figurate erythema of infancy, which is also considered a variant of erythema annulare, is characterized histologically by a dermal inflammatory infiltrate with neutrophils and leukocytoclasis without vasculitis.

**Figurate Erythemas With Granulomas**

Two entities, granuloma annulare and sarcoidosis, can manifest clinically with annular figural erythema and display granulomatous changes on histology. Borderline and tuberculoid leprosy may also occasionally take this clinical form.

Granuloma annulare is a self-limited skin disease of uncertain etiology that may be a nonspecific reaction to contact with a variety of agents. Histology has identified 3 variants: a granulomatous “palisaded” form, an interstitial (or incomplete) type, and a deep (or nodular) one. In the superficial variant, which differs from the deep one only in the location of the granulomas, palisaded histiocytes surround areas of degenerated collagen (Figure 12), where the presence of mucin can be revealed by special stains (Alcian blue or colloidal iron). A lymphocytic and eosinophilic inflammatory infiltrate can be observed. This palisaded form of granuloma annulare, unlike necrobiosis lipoidica, usually does not contain plasma cells. In the interstitial variant, in contrast, macrophages can be found between collagen bands, and palisaded granulomas do not form. The deep form is characterized by subcutaneous
granulomas with necrobiosis, and lesions are nodular rather than annular.\textsuperscript{42}

Cutaneous sarcoidosis, which varies greatly in clinical presentation, may manifest plaques that coalesce, coming to resemble annular or circinate lesions.\textsuperscript{43} The histologic pattern is the characteristic one for this disease regardless of which tissues are affected; observations include nonnecrotizing epithelioid granulomas without the involvement of nerves, vessels, or adnexal epithelial structures (Figure 13). A scant lymphocytic inflammatory infiltrate accompanies the “naked” granulomas. So-called asteroid bodies, Schaumann bodies, or birefringent calcium oxalate or calcium carbonate crystals are nonspecific findings that may aid diagnosis. The clinical and histologic differential diagnosis of cutaneous sarcoidosis is very wide ranging.\textsuperscript{44}

Borderline and tuberculoid leprosies share a histologic profile characterized by the presence of epithelioid granulomas arranged linearly (along nerves); CD4+ T cells are a major component of the accompanying lymphocytic inflammatory infiltrate.

**Figurate Erythemas With Plasma Cells**

Secondary syphilis, with its great variability of clinical expression, is known to masquerade as a number of other skin diseases. Although the most commonly observed lesions are scaly papules, secondary syphilis can also manifest with annular plaques that mimic erythema annulare centrifugum.\textsuperscript{45} Histologic examination shows a dermal inflammatory infiltrate with lymphocytes and plasma cells and a lichenoid lesion at the dermal-epidermal junction. In such cases, the marked epidermal hyperplasia of the papular lesions, with formation of pustules, will not be present. Staining with silver compounds or immunohistochemistry may detect the presence of spirochetes.

**Neoplastic Figurate Erythemas**

The presentation of mycosis fungoides, the most common of the primary cutaneous T-cell lymphomas, is variable, and like syphilis, it is considered a great imitator. To date, 10 cases manifesting as annular erythemas have been described.\textsuperscript{46-48} No distinctive histologic features have been identified to differentiate these lesions from those found in other contexts.

Finally, we mention that several visceral tumors (carcinomas)\textsuperscript{49} and hematologic malignancies (lymphomas and leukemias)\textsuperscript{5,6,50,51} can be associated with figurate skin lesions and resemble erythema annulare centrifugum. Likewise, so-called inflammatory breast carcinoma (invasion of superficial dermal lymph vessels in the skin over the gland) may also manifest with an annular plaque.\textsuperscript{52}

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**