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Case History

A 63-year-old woman presented with a 7 mm red shiny to scaly and crusty papule on right anterior thigh. A shave biopsy was performed.

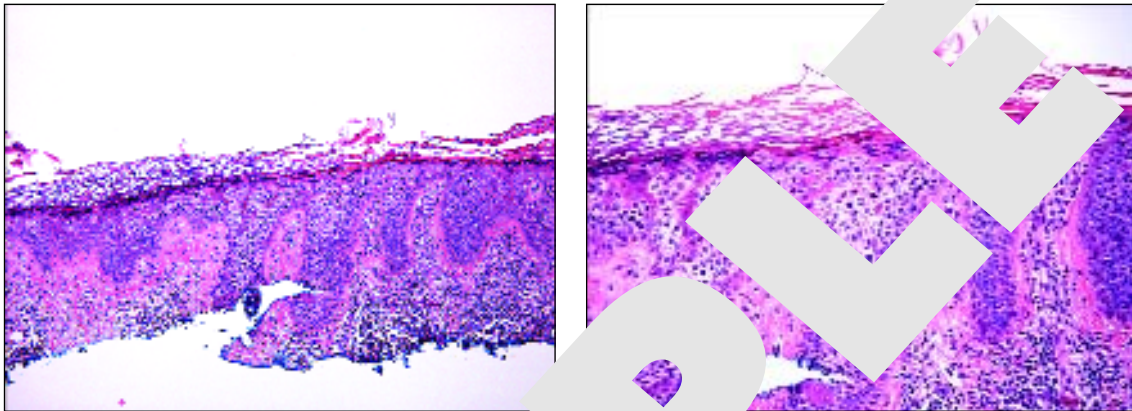


Figure 1

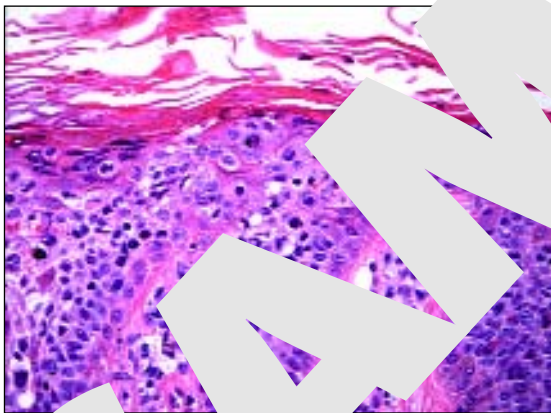


Figure 2

central area of full thickness epidermal atypia flanked laterally by areas showing pagetoid spread is noted. The total loss of polarity/maturation associated with the full thickness atypia is a diagnostic feature of squamous cell carcinoma *in situ* (100X).

Figure 2: The epidermis contains pagetoid cells and nests of atypical cells in all layers of epidermis (100X).

Figure 3: Higher magnification shows atypical cells with enlarged and pleomorphic nuclei, prominent nucleoli and abundant clear cytoplasm. Hyperkeratosis and focal parakeratosis is present (400X).

Diagnosis

Pagetoid squamous cell carcinoma *in situ*.

Commentary

Pagetoid squamous cell carcinoma *in situ* is a histopathological variant of squamous cell carcinoma *in situ* (SCCIS). It was originally described as a “precancerous dermatosis” by Bowen in 1912.¹ The etiology of SCCIS is believed to be ultraviolet light in sun-exposed skin and chemicals such as arsenic in non-sun-exposed parts. Arsenic is used in a variety of medications as well as insecticides, fungicides, and weed-killers and may contaminate natural water supplies.²

Clinical Features

SCCIS is mostly a disease of white-skinned races. It is more common in the middle-aged and the elderly.³ Despite the well-documented predilection for sun-exposed skin, any site (including the nail beds) may be affected. Lesions are usually single and typically present as slow growing, persistent, discrete patches that measure from a few millimeters to several centimeters in diameter.³ Clinically, the lesions often appear erythematous and scaly or crusted, and may resemble psoriasis, eczema, mammary Paget’s disease, extramammary Paget’s disease, and superficial basal cell carcinoma.^{3,4} Although pigmentation is rare, it may be present in anogenital lesions, which is a source of confusion with malignant melanoma.³

Histopathology

Complete disorganization of the epidermal architecture with dyskeratosis, loss of maturation and polarity is seen in a typical case of SCCIS. This full-thickness atypia is marked by nuclear enlargement, pleomorphism, and mitotic figures in all layers of epidermis. Atypical mitotic figures may be present. Acanthosis, hyperkeratosis and parakeratosis are usually seen.

Not uncommonly, SCCIS shows morphologic variations to this classic histology, which makes the diagnosis more challenging to pathologists. These variations are reflected in the following subtypes:³

- Psoriasiform: Acanthosis and parakeratosis with broad and occasional fused rete ridges.
- Atrophic: The epidermis is atrophic similar to atrophic actinic keratosis but with full-thickness atypia.
- Verrucous hyperkeratotic: Church spire papillomatosis and marked hyperkeratosis.
- Acantholytic: Dyscohesion of atypical epidermal keratinocytes.
- Pagetoid: Pagetoid SCCIS is characterized by multiple intraepidermal keratinocyte nests with clear or light eosinophilic cytoplasm which is the result of cytoplasmic accumulation of glyco-

gen. The glycogen stains with PAS but is removed from cells after treatment with diastase (PASD-labile). The nests are present in various layers of the epidermis, especially the more superficial layers, and show cellular atypia. However, the lesion may lack the full thickness atypia characteristic of other histological subtypes of SCCIS. This variant is part of the so-called 'Borst-Jadassohn intraepithelial epithelioma', a designation of the past which comprises different clinicopathologic entities that share this morphologic pattern.⁵

Histopathologic Differential Diagnosis

The differential diagnosis of pagetoid cells within the epidermis includes pagetoid SCCIS, mammary and extramammary Paget's disease, malignant melanoma *in situ*, solitary pagetoid reticulosis, clonal seborrheic keratosis, sebaceous carcinoma, Merkel cell carcinoma, clear cell papulosis, Langerhans' cell histiocytosis, porocarcinoma, and epidermotropic eccrine carcinoma.⁶ In most cases, clinical correlation and other histologic features can help to establish a definitive diagnosis. Here we discuss common entities that closely mimic pagetoid SCCIS histopathologically.

Mammary or extramammary Paget's disease is characterized by atypical Paget's cells with large vesicular nuclei, prominent nucleoli, and abundant slightly eosinophilic to clear mucin-rich cytoplasm infiltrating the epidermis as solitary units or in small nests (**Figure 4a**). The cells are frequently but not invariably positive for mucicarmine and PAS-D. Therefore, negative results of these two stains alone neither preclude Paget's disease nor confer a diagnosis of pagetoid SCCIS. Immunohistochemistry is helpful in such cases. Paget's cells show positivity for cytokeratin 7 (CK 7), CAM 5.2, EMA, and CEA in most of the cases. Although EMA and CEA are typically positive in Paget's cells, these markers are not very specific and may be positive in cases of SCCIS including pagetoid SCCIS.⁶ In contrast, CK 7 appears to be a more specific marker for Paget's cells (**Figure 4b**). It is almost invariably positive in mammary and extramammary Paget's disease but negative in most cases of pagetoid SCCIS⁶ albeit with rare exceptions documented in case reports.⁷ Similarly, CAM 5.2 is positive in Paget's disease and negative in pagetoid SCCIS.⁶ Therefore, CK7 and CAM 5.2 may be the most useful immunohistochemical markers in distinction between pagetoid SCCIS and Paget's disease.

Pagetoid malignant melanoma *in situ* shows lentiginous and nested atypical junctional melanocytic proliferation with upward migration of atypical melanocytes in single units or as nests of variable size within the epidermis (**Figures 5a** and **5b**). The lesion may or may not be pigmented. The histological pattern may resemble pagetoid SCCIS but with the aid of immunohistochemistry, it is a rather easy distinction since the pagetoid melanocytes in pagetoid melanoma *in situ* exhibits immunoreactivity to S100, HMB-45, and Melan-A whereas atypical cells in pagetoid SCCIS are invariably negative.⁸

Solitary pagetoid reticulosis is an intraepidermal variant of mycosis fungoides, previously referred to as Woringer-Kolopp disease. It clinically presents as a single psoriasiform, crusty or hyperkeratotic patch, typically on the distal limb,⁹ and are often mistaken as squamous neoplasms. The atypical pagetoid lymphocytes (**Figure 6a**) are positive for lymphoid marker, LCA. Immunophenotypic studies have disclosed the malignant lymphocytes to be CD3+ T cells (**Figure 6b**) and either CD4+, CD8+, or double-negative for both epitopes. T-cell receptor gene rearrangements may be demonstrated.

Clonal seborrheic keratosis is a histological variant of seborrheic keratosis. It is characterized by intraepidermal nests or clusters of small, uniformly bland keratinocytes with pale cytoplasm (**Figures 7a** and **7b**). Since no evidence for clonal proliferation has been shown in these lesions,¹⁰ the alternative term 'nested' seborrheic keratosis has been proposed. The key to differential diagnosis is the lack of significant atypia in clonal seborrheic keratosis as opposed to the atypical pagetoid cells/nests and areas of full thickness epidermal atypia in pagetoid SCCIS.

In summary, the clinical and morphologic findings can narrow the differential diagnosis of pagetoid SCCIS in the majority of cases. However, careful morphologic observation and immunohistochemistry may be needed in occasional close mimickers. Although pagetoid SCCIS shows focal pagetoid involvement of the epidermis, it is often associated with adjacent areas of full thickness epidermal atypia which is a very useful distinguishing feature from the other aforementioned differential diagnostic entities.

Clinical Course

Although SCCIS follows a generally favorable course, approximately 5% of the cases do progress to invasive carcinoma, of which 30% have metastatic potential.¹¹

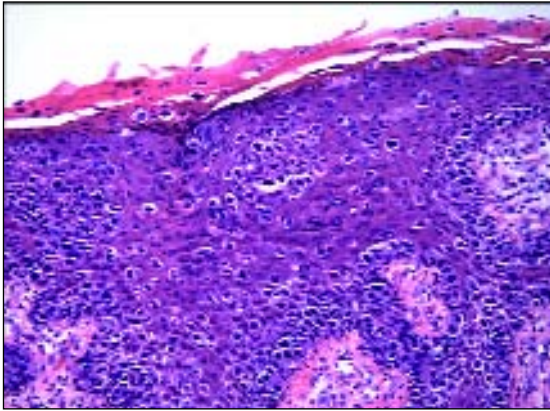


Figure 4a

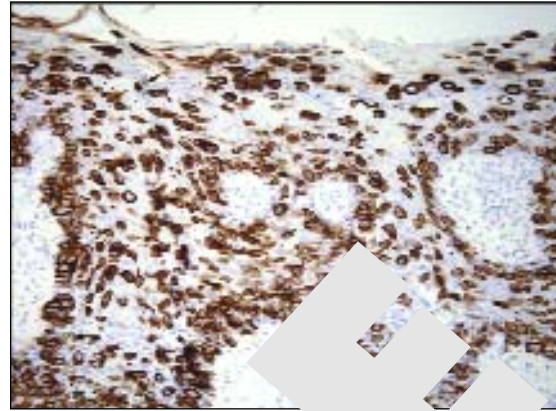


Figure 4b

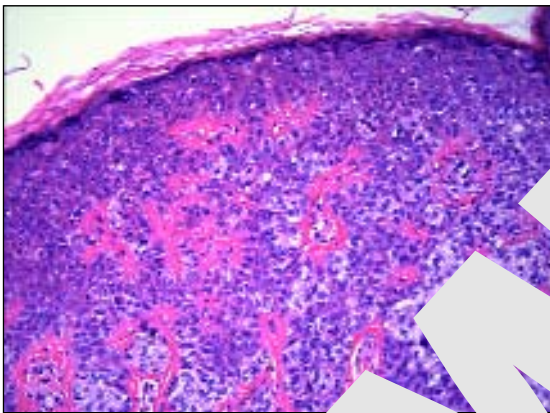


Figure 5a

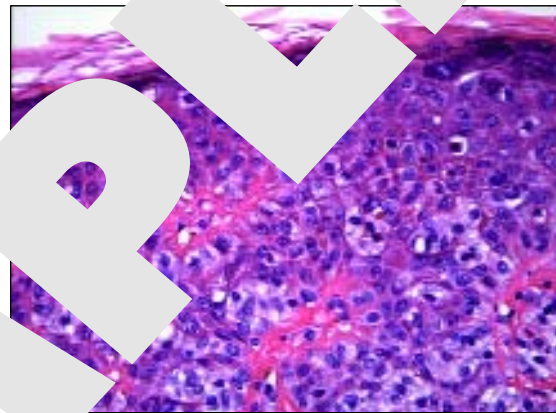


Figure 5b

Figures 4a: Extramammary Paget's disease. Paget's cells with pleomorphic nuclei, prominent nucleoli, and cytoplasm infiltrate the epidermis (X200).

Figure 4b: Primary Paget's disease. A Cytokeratin 7 stain highlights the Paget's cells

Figure 5a: Lentiginous melanoma *in situ*. Atypical junctional melanocytic nests with upward migration of pagetoid cells to superficial layers of epidermis (X200).

Figure 5b: Pagetoid malignant melanoma *in situ*. There are atypical pagetoid cells with prominent nucleoli and artifactual cytoplasmic clearing scattered within the epidermis as single cells or in nests of variable size (X400).