Mammary and extramammary Paget's disease

J Lloyd, A M Flanagan

Abstract
Mammary and extramammary Paget's disease are uncommon intraepithelial adenocarcinomas. Both conditions have similar clinical features, which mimic inflammatory and infective diseases. Histological diagnostic confusion can arise between Paget's disease and other neoplastic conditions affecting the skin, with the most common differential diagnoses being malignant melanoma and atypical squamous disease. The glandular differentiation of both mammary Paget's disease and extramammary Paget's disease is indicated by morphological appearances, the presence of intracellular mucin in many cases, and positive immunohistochemical staining for glandular cytokeratins, epithelial membrane antigen, and carcinoembryonic antigen. This article provides an overview of mammary and extramammary Paget's disease and discusses recent evidence regarding the cell of origin. The concepts of primary and secondary Paget's disease are presented and the differential diagnosis is discussed with reference to immunohistochemical markers that might be of diagnostic value.
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Mammary Paget's disease was first described by James Paget in 1874.[1] He stated that the malignancy originated in large lactiferous ducts from where it extended into the overlying epidermis. He considered that the changes in the skin preceded and induced malignant change in the underlying breast tissue. Extramammary Paget's disease was originally described in 1889 by Crocker,[2] who reported lesions on the scrotum and penis, with histological features similar to those described by Paget. Crocker believed the tumour to be derived from sweat and sebaceous glands or hair follicles. Dubreuilh described the first case of vulval extramammary Paget's disease in 1901. Mammary and extramammary Paget's disease have many similar features, in particular their gross and histological resemblance to a variety of other skin conditions. This article provides an overview of both diseases and the likely cell of origin. The differential diagnosis is discussed with reference to immunohistochemical markers that might be of diagnostic value.

Cell of origin in mammary and extramammary Paget's disease
Mammary Paget's disease and extramammary Paget's disease are neoplastic conditions, in which there is intraepithelial (usually intraepidermal) infiltration by neoplastic cells showing glandular differentiation. In recent years, there has been controversy as to the cell of origin in Paget's disease, particularly in the extramammary form.

The prevailing view is that most, if not all, cases of mammary Paget's disease originate from in situ or invasive ductal carcinoma in the underlying breast tissue. The origin of extramammary Paget's disease is less well defined, and the findings in mammary Paget's disease were initially extrapolated in an attempt to explain the development of the extramammary form. It was therefore proposed that all cases of extramammary Paget's disease arose as epidermotropic spread from an in situ or invasive neoplasm arising in an adnexal gland within the dermis, analogous to mammary Paget's disease arising from ductal carcinoma in situ.

However, unlike mammary Paget's disease, where the proportion of cases in which an associated neoplasm can be demonstrated is high, the extramammary form is associated with an underlying in situ or invasive neoplasm in a much smaller proportion of cases (9–32% in several small studies).[3–11] On average, 25% of cases of extramammary Paget's disease are said to have associated neoplastic disease (in adnexal structures or in organs with a contiguous epithelial lining), although the frequency varies with the site of the disease (see below). Many workers, having assumed that extramammary Paget's disease must, like the mammary form, be associated with an underlying neoplasm in most cases, proposed reasons for the low rate of detection of associated neoplastic disease in extramammary Paget's disease that include: (1) in situ disease of apocrine glands may manifest only as microscopic foci, confined to sweat gland ducts, and might be overlooked in histological examination[9 10]; (2) failure to detect a small, in situ or invasive neoplasm in an adnexal gland, the result of inadequate histological sampling.

Conversely, it was argued that the reason a neoplasm could not be demonstrated in many cases of extramammary Paget's disease was that, unlike mammary Paget's disease, most cases arise primarily within the epidermis. Hence, many cases of extramammary Paget's disease, purporting to demonstrate associated neoplastic disease in the skin, were said to be misdiagnoses based on the following: (1) Paget's cells from the epidermis may infiltrate and colonise sweat gland ducts and hair follicle epithelium. This colonisation was then indistinguishable from primary intraductal carcinoma of the sweat gland. (2) Paget's disease arising primarily within the epidermis may,

Department of Histopathology, Northwick Park and St Mark's NHS Trust, Watford Road, Harrow, Middlesex HA1 3UJ, UK
J Lloyd

Imperial College School of Medicine (St Mary's Campus), Norfolk Place, London W2 1PG, UK
A M Flanagan

Correspondence to:
Dr Lloyd
8spook8@excite.com

with time, progress from intraepidermal neoplasia (in situ disease) to dermally invasive adenocarcinoma (in a fashion analogous to invasive malignant melanoma arising from superficial spreading malignant melanoma).[12][13] This might subsequently metastasise to local lymph nodes and distant sites. Therefore, invasive carcinoma resulting from dermal invasion of epidermal Paget's cells might be misinterpreted as a primary adnexal carcinoma, which had given rise secondarily to extramammary Paget's disease.[9] In cases with extensive dermal invasion, it may be impossible to prove whether the tumour originated within the epidermis or within an adnexal structure.

The current theory is that extramammary Paget's disease arises as a primary intraepidermal neoplasm in most cases. The tumour cells are proposed to originate either from the intraepidermal cells of apocrine gland ducts or from pluripotent keratinocyte stem cells. The few cases of mammary Paget's disease in which a breast neoplasm cannot be detected are felt to have a similar explanation.[14] Such cases are sometimes referred to as "primary Paget's disease" to distinguish them from the small number of cases that arise as "secondary" spread from an underlying neoplasm in a dermal adnexal gland or a local organ with contiguous epithelium.[9]

The immunohistochemical profile of Paget's cells is well characterised (see below), and indicates that they show definitive glandular differentiation. It has become clear that the immunohistochemical profiles of mammary and extramammary Paget's disease are similar, but subtle differences exist that might reflect the different cell of origin in each case. Cases remain, mainly of extramammary Paget's disease, where the site of origin is still in question, but regardless of location, Paget's cells are always adenocarcinoma cells.

Mammary Paget's disease
Mammary Paget's disease occurs exclusively on the nipple/areola complex from where it may spread on to surrounding skin. The clinical appearance is usually a demarcated, thickened, eczematoid, erythematous weeping or crusted lesion with irregular borders. Nipple discharge and ulceration may occur. An associated breast tumour may be palpable. A small proportion of cases of mammary Paget's disease are clinically occult and only detected histologically when a representative section of the nipple and areola is submitted from a mastectomy. Differential clinical diagnoses include generalised inflammatory skin conditions such as eczema and psoriasis, as well as erosive adenomatosis, a condition specific to the nipple.

Mammary Paget's disease accounts for 2–3% of neoplastic conditions of the breast and in most cases (82–92% in several studies) tumour cells have spread to the skin of the nipple and areola from underlying invasive carcinoma or ductal carcinoma in situ.[15–17] Rare cases appear to have originated primarily within the nipple epidermis. The neoplasm associated with mammary Paget's disease, which may or may not be palpable, is usually centrally located (within 2 cm of the areola) but occasionally may be more peripherally sited.[15][16] In cases where a mass is palpable, invasive carcinoma is likely to be found. Conversely, cases of mammary Paget's disease with no palpable mass are more likely to have ductal carcinoma in situ only (66% of cases in one study).[16] Neoplastic disease within the breast is said to be more commonly multifocal if mammary Paget's disease is present.

Mammography or ultrasound (as appropriate) is advocated in all cases of mammary Paget's disease to locate an associated tumour, but these investigations can fail to identify abnormal breast tissue in patients with no palpable mass, and may underestimate the extent of multifocal disease.[15][16][18] It is claimed that patients with mammary Paget's disease and a palpable mass have a much greater incidence of invasive carcinoma, multifocal lesions, and lymph node metastases, and a worse survival than patients in whom the tumour does not show epidermal spread.[16] However, other studies compared patients with invasive carcinoma with and without mammary Paget's disease and found that the most important prognostic factor was the presence or absence of axillary metastases, rather than the presence of skin involvement.[19]

Mammary Paget's disease associated with in situ or invasive carcinoma is generally treated by excision of the nipple/areola complex, but surgery is ultimately based around the appropriate means of complete excision of the associated intramammary disease.[20][21] As a consequence of the claimed high prevalence of multifocal disease, most patients with mammary Paget's disease associated with neoplastic disease of the breast undergo mastectomy (with or without axillary sampling) rather than breast conserving surgery (that is, wide local excision of tumour with excision of the nipple/areola complex).[20] Conservative surgery (excision of the nipple/areola complex) with adjuvant radiotherapy may be possible in selected cases.[20][22] Radiotherapy alone has been proposed as a viable alternative to surgery for the rare cases that lack evidence of associated neoplastic disease in the underlying breast tissue.[22–24]

Mammary Paget's disease has been reported in the male breast with no evidence that the disease behaves differently, although the numbers of cases reported are small.[25]

Extramammary Paget's disease
The most common presenting symptom in extramammary Paget's disease is pruritis. The clinical appearance is similar to mammary Paget's disease. Lesions occasionally show hyperpigmentation or hypopigmentation.[26] In the anogenital region atypical appearances occur; ulceration or areas of leukoplakia have been reported. Extramammary Paget's disease is a slow growing tumour and the appearances of long standing lesions may be modified by repeated traumatisation/excoriation or superimposed infection. An associated tumour may be palpable. The features can be so non-

specific that misdiagnosis as an inflammatory or infective skin condition (eczema, psoriasis, moniliasis) is common, and lesions may be advanced before appropriate treatment is instigated.

Extramammary Paget's disease is an uncommon neoplasm, which although it occurs most commonly in the anogenital region, can arise in any area of skin or mucosa. This disease arises most frequently in postmenopausal women and on the vulva. Even so, extramammary Paget's disease comprises 2% or less of primary vulval neoplasms and extramammary Paget's disease arising in other sites is even more rare. There are reports of the disease arising in other apocrine gland rich areas, such as axilla and ear, with a case on the eyelid being associated with Moll's gland carcinoma.[27–29] Extramammary Paget's disease of the external male and female genitalia may be associated with neoplasms arising in the bladder and urethra, and in the prostate in men. Extramammary Paget's disease of the perianal skin is often associated with colorectal neoplasia. Occasional cases have involved the skin of the extremities and abdomen. Cases have occurred in the squamous epithelial lining of an ovarian teratoma and in the lining of an epidermal cyst.[30 31]

VULVAL EXTRAMAMMARY PAGET'S DISEASE
As previously discussed, it is currently believed that most cases of vulval extramammary Paget's disease are primary; that is, arising within the epidermis, and very few are associated with cutaneous sweat gland tumours.[3 9 32] In cases where there is a prominent dermal invasive component, it may be impossible to prove the primary site of origin of the tumour. A new variant of "mammary like" cutaneous glands, which combines morphological features of mammary, eccrine, and apocrine glands, and occurs predominantly in the interlabial sulcus on the vulva, has also been proposed as the site of origin of sweat gland derived tumours from which extramammary Paget's disease arises.[33] It is suggested that the existence of these glands unifies mammary and extramammary Paget disease as well as other mammary type lesions occurring in the vulval region (such as fibroadenoma, postpartum functioning mammary glands).[34]

Vulval extramammary Paget's disease has been described in association with endometrial, endocervical, and vaginal as well as vulval (for example arising within Bartholin's gland), urethral, and bladder neoplasms.[34–38]

This phenomenon of epidermal colonisation by cells from a neoplasm originating within local internal organs with epithelial linings contiguous with the affected skin is described in many articles as spread from "internal malignancy". This nomenclature is used to distinguish these cases, where an underlying neoplasm can be identified, from cases where the Paget's disease is believed to have arisen either primarily within the epidermis or from a tumour local to the skin (for example, a skin appendage tumour).

Rare reports exist of extramammary Paget's disease associated with distant tumours arising in organs without a direct epithelial connection to the affected epidermis. Examples include ovarian carcinoma, bile duct carcinoma, hepatocellular carcinoma, and renal cell carcinoma.[38 39] Vulval extramammary Paget's disease has also been described in association with breast carcinoma.[40] It is likely that such cases simply represent synchronous coincidental neoplasms. No evidence exists in any of the described cases that the Paget's cells originated from the internal malignancy.

AXILLARY EXTRAMAMMARY PAGET'S DISEASE
Axillary extramammary Paget's disease may, like vulval disease, arise within the epidermis or from neoplasms in the local apocrine glands, but exclusion of neoplastic disease in the breast tissue is mandatory before a diagnosis of primary extramammary Paget's disease is made in this site. Analysis of c-erbB-2 expression may be of use in this differential diagnosis (see below).

PERIANAL EXTRAMAMMARY PAGET'S DISEASE
Perianal extramammary Paget's disease is more rare than vulval disease but is strongly associated with adenocarcinoma of the anus and colorectum.[10] Unlike vulval extramammary Paget's disease, 70–80% of cases of perianal disease arise secondary to invasive malignancy in the anus, rectum, or colon. Thorough investigation of this region is mandatory if a diagnosis of perianal Paget's disease is given.

PAGET'S DISEASE OF THE MALE GENITALIA
In common with perianal extramammary Paget's disease, disease of the male genitalia is thought to be more frequently associated with internal malignancy (for example, urethral, bladder, prostatic, and testicular neoplasms) than is vulval extramammary Paget's disease.[35 36 41]

MANAGEMENT OF EXTRAMAMMARY PAGET'S DISEASE
The most appropriate management of primary extramammary Paget's disease at any site is local surgical excision, ideally with a 1 cm margin of normal skin.[20] Extensive vulval disease has been managed with superficial "skinning" vulvectomy and split skin grafting. Small recurrences/foci of residual disease (or more extensive lesions in those unsuitable for surgery) may be treated by laser vaporisation. In patients unfit for radical surgery, radiotherapy is proposed as alternative treatment, as long as invasive disease has been excluded.[20 42]

Extramammary Paget's disease is often multifocal and in many cases it has been demonstrated histologically that the disease extends beyond the visible lesion—for example, primary vulval extramammary Paget's disease can spread into urethral, upper vaginal, and cervical epithelia.[43–45] Multiple surgical excisions may be required to control residual and recurrent disease.[3 4 20] Intraoperative frozen sectioning has been used to improve the rates of complete excision and improve prognosis.

However, the diagnostic accuracy of intraoperative frozen sectioning can be poor.[46][47] One study found a 31% inaccuracy rate, which was comparable with the inaccuracy of simple visual assessment. Another study has reported that there was no difference in recurrence rate whether or not there were negative surgical margins.[8] The multifocal nature of the condition might account for this finding.

The management of extramammary Paget's disease associated with an underlying neoplasm is, as with mammary Paget's disease, directed towards the appropriate treatment for the associated neoplasm. Radical surgery with or without adjuvant radiotherapy is advocated for patients with an associated adenocarcinoma.[20][48][49]

In general, the prognosis for primary extramammary Paget's disease confined to the epidermis is excellent. Dermal invasion is thought to be present in up to 20% of cases of primary intraepidermal extramammary Paget's disease, although it might not be detected if sampling is not rigorous.[9][10] Primary extramammary Paget's disease has a worse prognosis in the presence of dermal invasion, and it has been suggested that the prognosis depends on the depth of dermal invasion (analogous to early stromal invasion or superficial dermal invasion in squamous dysplasia).[9] Cases of primary extramammary Paget's disease showing only microscopic invasion (< 1 mm dermal invasion) are proposed to have a more favourable prognosis than lesions showing deeper invasion, but the numbers of cases available for long term study in the literature are small.[9][10] At present, there are insufficient data with which to predict the behaviour of invasive extramammary Paget's disease based on depth of invasion, although current data suggest that microscopic invasion does not adversely affect prognosis. In contrast, prognosis decreases substantially even in microscopically invasive extramammary Paget's disease if lymphovascular invasion is present. Five year survival is 0% in the presence of inguinal lymph node metastases.[20] Lengthy follow up is advocated for all cases of primary extramammary Paget's disease, with investigations to exclude associated in situ or invasive malignancy, particularly in perianal and male genital disease.

The prognosis for extramammary Paget's disease secondary to underlying neoplasia is worse than when the disease has arisen primarily within the epidermis. It depends on the prognosis of the underlying carcinoma.

Histopathology: Paget's cells[50][51]
The histopathological findings are similar in mammary and extramammary Paget's disease. Paget's cells are large cells with abundant basophilic or amphophilic, finely granular cytoplasm, which tend to stand out in contrast to the surrounding epithelial cells. On close inspection the nucleus is usually large, centrally situated, and sometimes contains a prominent nucleolus. Pronounced nuclear atypia and pleomorphism are present. Signet ring cells might be present in small numbers and mitotic figures are frequent. The Paget's cells might be dispersed singly or form clusters, glandular structures, or solid nests. There may be infiltration into upper strata of the epidermis, but most cells are concentrated in the lower portion, often being observed in the pilosebaceous apparatus. Cells might be present in sweat gland ducts, leading to confusion as to whether the lesion has arisen within the epidermis or has spread from a local apocrine neoplasm. A dense inflammatory infiltrate is often seen associated with the epidermal malignancy.

In > 90% of cases of extramammary Paget's disease the tumour cells contain cytoplasmic mucin, staining positively with mucicarmine and periodic acid Schiff reagent. Only 40% of cases of mammary Paget's disease show any intracellular mucin and staining is generally weaker than in extramammary disease.

Cytological examination of skin scrapings from lesions of Paget's disease reveals single malignant cells with vacuolated cytoplasm and eccentric nuclei, three dimensional cell aggregates, and acinar groups consistent with glandular differentiation. However, the material obtained is variably cellular and often shows a background of keratinous debris, which may lead to confusion with inflammatory skin conditions or squamous neoplasia.[52] Hence, it might be more appropriate to biopsy lesions.

Differential histological diagnosis
The distinctive histological pattern of epidermal infiltration of Paget's cells has led to the use of the term "pagetoid spread" to indicate any condition where cells are distributed singly and in small groups throughout an epithelial layer. Other pathological conditions in which this pattern is seen include superficial spreading malignant melanoma, Bowen's disease, mycosis fungoides, Langerhans cell histiocytosis, and Spitz naevus. Toker cells are normal epidermal cells that resemble Paget's cells (see below). All these conditions can affect skin in the areas in which Paget's disease has been reported, and should be considered in the differential diagnosis. In most cases the correct diagnosis can be reached with careful morphological evaluation and the help of a panel of immunohistochemical markers.

PAGETOID BOWEN'S DISEASE AND PAGET'S DISEASE
Long standing lesions of Paget's disease often show pronounced hyperkeratosis and parakeratosis with epidermal hyperplasia, elongation of rete ridges, and reactive atypia of the keratinocytes. Paget's disease can be misdiagnosed as Bowen's disease (squamous cell carcinoma in situ) if it is not appreciated that the infiltrating atypical cells are glandular and not squamous in origin. Dyskeratotic cells have been said to be a useful pointer towards Bowen's disease but can also be seen in Paget's disease in which there is associated squamous atypia.[50] Cases have been reported where extramammary Paget's disease coexists with VIN3 (high grade vulval intraepithelial neoplasia), but this is unusual.[53] Bowen's disease can show a pagetoid pattern of epidermal involvement. Intracellular

mucin, signet cells, and glandular structures are useful features to distinguish Paget's disease, being absent in Bowen's disease. In cases where morphological features of glandular differentiation are absent, immunohistochemical staining (Cam 5.2, EMA, CEA positive in Paget's disease) will usually resolve the problem.[54–63]

The atypical cells in superficial spreading malignant melanoma show prominent nesting along the dermoepidermal junction, whereas those in Paget's disease are usually distributed more diffusely. The cells of Paget's disease and melanoma can both contain melanin granules and, although the granules are generally coarser in Paget's disease, this is not a sound discriminatory diagnostic feature. Acinar formation is not seen in melanoma and there is no intracellular mucin present. Reactive epidermal atypia is common in Paget's disease but rare in melanoma. Immunohistochemical markers S100 and HMB-45 are positive in most cases of melanoma.[56] HMB-45 does not label Paget's cells but S100 is positive in a proportion of cases of mammary Paget's disease and may very occasionally be positive in extramammary disease.[64] Melanocytes are not labelled with the antibodies commonly used to identify Paget's cells (Cam5.2, anti-EMA, anti-CEA).[65]

MYCOSIS FUNGOIDES AND PAGET'S DISEASE

The infiltrating neoplastic T cells in mycosis fungoides have characteristic features with large convoluted (cerebriform) nuclei set in pale cytoplasm. Single cells often have a clear halo around them and may resemble Paget's cells. Aggregates of atypical lymphocytes (Pautrier microabscesses) may be seen, which can be confused with glandular clusters. A lymphocytic dermal infiltrate is often seen in cases of mycosis fungoides and Paget's disease, and is not a useful discriminant. Immunohistochemical staining for T cell markers (CD3, UCHL-1) is positive in mycosis fungoides.

LANGERHANS CELL HISTIOCYTOSIS AND PAGET'S DISEASE

The nuclei of the atypical cells in the various forms of histiocytosis are large and set in abundant pale cytoplasm. They are described as reniform or "bean shaped" unlike the nuclei in Paget cells. Immunohistochemical markers CD1a, HLA-DR, and S100 are positive in histiocytosis.

TOKER CELLS AND CLEAR CELL PAPULOSIS AND PAGET'S DISEASE[66 67]

Toker cells are intraepidermal cells seen in 10% of normal nipples, which have also been described in fibroepithelial polyps at other sites. They have abundant clear cytoplasm and small, uniform, eccentric nuclei. They are sited predominantly in the basal epidermis around the orifices of lactiferous ducts, but may show hyperplasia, extending into the upper strata

and forming small aggregates, leading to confusion with mammary Paget's disease. It has been proposed that they are the cells of origin in cases of mammary Paget's disease that lack an associated invasive carcinoma or focus of ductal in situ carcinoma.[66] Toker cell hyperplasia has been described in association with a case of mammary Paget's disease, which affected only the areola, and not the nipple, and which lacked an associated neoplasm in the affected breast.[67] On close inspection, Toker cells should be easily distinguishable from the pleomorphic cells with atypical nuclei that characterise Paget's disease. Clear cell papulosis shows similar histological features to (and may be analogous to) Toker cell hyperplasia and affects extramammary skin along the distribution of the milk line. It can therefore be confused with extramammary Paget's disease.[68] The immunohistochemical profile of Toker cells overlaps with that of Paget's cells such that morphological correlation is essential for diagnosis.[66]

Immunohistochemistry

Immunohistochemistry has been useful not only in the diagnosis of Paget's disease but also in attempting to clarify the cell of origin in Paget's disease. In addition to similar histological features, tumour cells in mammary and extramammary Paget's disease show similar immunophenotypes. However, minor variations in antigen expression between the two disease forms exist and, furthermore, it is becoming apparent that there are also antigenic differences between primary intraepidermal Paget's disease and Paget's disease that has spread from an associated internal adenocarcinoma. Differences exist, particularly with regard to markers for GCDFP-15 and cytokeratins 7 and 20 (see below), which lend support to the theory of a dual origin for Paget's disease. These markers might prove to be useful in predicting whether an associated internal malignancy is likely to be found when a biopsy diagnosis of Paget's disease is made. However, it is not possible to distinguish between intraepidermal Paget's disease and Paget's disease arising from a local sweat gland neoplasm using immunohistochemical markers because virtually all Paget's cells show apocrine differentiation in such cases.[69]

CYTOKERATINS

Cytokeratins are water insoluble, fibrous proteins present in almost all epithelia. At least 20 subclasses exist, based on molecular weight and pH value.

Cam5.2 is a combination of antibodies that labels low molecular weight cytokeratins and highlights Paget's cells in 70–90% of cases of mammary and extramammary Paget's disease, whereas the adjacent epidermis is not labelled because it expresses high molecular weight cytokeratins. Paget's cells do not react with antibodies to high molecular weight cytokeratins. Other antikeratin antibodies are claimed to be more sensitive than Cam 5.2.

Cytokeratin 7 (CK7) is widely distributed in neoplastic and non-neoplastic tissue. In the

skin it is found in sweat gland acini but not epidermis or hair follicle epithelium. It has been found to be a sensitive, although not specific, marker for mammary and extramammary Paget's disease.[70][71] A small number of cases do not label with anti-CK7, commonly those with an underlying malignancy in an internal organ.[9][10] Anti-CK7 also marks some Toker cells and Merkel cells so morphological assessment of the labelled cells is necessary.[66]

In contrast to CK7, cytokeratin 20 (which is found in most gastrointestinal and urothelial carcinomas) is found more frequently in cases of extramammary Paget's disease with an underlying carcinoma than cases of primary intraepidermal disease.[10][72] Thus, the pattern of cytokeratin expression may allow the presence or absence of associated internal malignancy to be predicted.[9][10]

GROSS CYSTIC DISEASE FLUID PROTEIN

Gross cystic disease fluid protein (GCDFP-15 or BR-2) is present in cyst fluid in fibrocystic disease of the breast and is a marker of apocrine epithelium (including normal apocrine glands, apocrine metaplasia in fibrocystic disease, and apocrine carcinomas). GCDFP-15 is strongly expressed in cases of vulval and perianal extramammary Paget's disease without an underlying internal malignancy, and much less frequently in cases with an associated malignancy.[9][10][69][72][73] However, GCDFP-15 expression does not exclude the presence of a dermal apocrine tumour.

HUMAN MILK FAT GLOBULE MEMBRANE ANTIGEN

Human milk fat globule membrane antigen (HMFG)/epithelial membrane antigen (EMA). EMA is a marker of most normal and neoplastic epithelia but it is also expressed by a variety of mesenchymal and lymphoid neoplasms. It is a glycoprotein present in human milk fat globule membranes. Most cases of mammary and extramammary Paget's disease are labelled by antibody to EMA. Squamous epithelium is not labelled. Monoclonal antibodies to HMFG are said to show greater epithelial specificity than those to EMA.[74]

CARCINOEMBRYONIC ANTIGEN

Carcinoembryonic antigen (CEA) is a glycoprotein normally detected in fetal epithelial cells but which is also strongly expressed in adenocarcinomas, particularly of the gastrointestinal tract and lung. Most cases of extramammary Paget's disease are strongly positive for CEA, particularly cases without an associated carcinoma. Only approximately 35% of cases of mammary Paget's disease label with anti-CEA antibodies.[59][60][69]

OESTROGEN AND PROGESTERONE RECEPTORS

In mammary Paget's disease, tumour cells generally show a similar immunohistochemical steroid receptor profile to the associated breast carcinoma. In contrast, only a few sweat gland derived tumours of the skin have been shown to express oestrogen receptors. Cases of extramammary Paget's disease are generally negative for steroid receptors.[75][76]

c-erbB-2

Overexpression of this oncogene correlates with gene amplification: in breast carcinomas it correlates with large tumour size, higher grade, and poorer prognosis, although it does not correlate with the presence of lymph node metastases. The gene encodes a transmembrane growth factor receptor of the tyrosine kinase family, related to epidermal growth factor receptor, and experimental amplification of the gene causes cellular transformation. Monoclonal antibodies to the protein react with most cases of mammary Paget's disease (90–100%) and the associated neoplasm in the breast. c-erbB-2 is detected in around 44% of cases of ductal carcinoma in situ, and is more commonly present in high grade (comedo and micropapillary) lesions. Only 16% of invasive ductal carcinomas are c-erbB-2 positive. Its high prevalence in cases of mammary Paget's disease is proposed to reflect a causal link between oncoprotein expression and epidermotropic spread, but might also reflect the fact that most cases of mammary Paget's disease are associated with higher grades of ductal carcinoma in situ. In extramammary Paget's disease, c-erbB-2 is less frequently detected (30–50% of vulval cases) and staining is weaker than in mammary Paget's disease. Hence, the protein is clearly not essential for epidermal spread. c-erb-B2 is never detected in normal epidermal cells.[77–80]

S100 AND HMB-45

S100 is an acidic calcium binding protein present in glial cells, Schwann cells, melanocytes, chondrocytes, adipocytes, and myoepithelial cells. It is useful in the differentiation between Paget's disease and melanoma. However, S100 expression may be seen in up to 25% of cases of mammary Paget's disease (a similar frequency to mammary carcinoma) and has been rarely described in extramammary Paget's disease. Therefore, S100 is best used in conjunction with HMB-45 when malignant melanoma is the differential diagnosis.[64] HMB-45 is a monoclonal antibody obtained from an extract of malignant melanoma. It marks activated/neoplastic melanocytes and other neural crest derived tumours as well as occasional carcinomas. HMB-45 does not react with Paget's cells in mammary or extramammary Paget's disease.

Cytogenetics

Only a few studies have looked at the genetics of Paget's disease. One study examined multiple tumour suppressor gene loci commonly involved in other human cancers but found no loss of heterozygosity in any of their 14 cases of extramammary Paget's disease.[81] In particular, bcl-2 expression was negative in all 14 cases and altered p53 expression was not found. Another group studied 34 cases of vulval extramammary Paget's disease and also concluded that p53 mutations were not involved in its pathogenesis.[80] In contrast, one study detected p53 expression in one third of cases of mammary Paget's disease.[82] Another series looked at the p53 protein concentration in

benign and malignant sweat gland tumours including 12 cases of extramammary Paget's disease, six of which showed positive staining for p53. They concluded that p53 mutations might play a role in a subset of sweat gland tumours, including extramammary Paget's disease.[83] p53 expression does not appear to have prognostic relevance in Paget's disease.[84]

c-erbB-2 oncogene expression has been discussed above. c-erbB-2 expression is increased in most cases of mammary Paget's disease (in which staining is similar to that seen in the associated intramammary neoplasm) and in fewer cases of extramammary Paget's disease, where staining is generally weaker. Other authors found no staining for c-erbB-2 in extramammary Paget's disease and consider c-erbB-2 expression to have no role in the pathogenesis of extramammary Paget's disease.

One study looked at expression of the ras p21 oncogene in mammary and extramammary Paget's disease. All cases of mammary Paget's disease (which were all associated with invasive carcinoma) reacted with the marker for p21. Cases of extramammary Paget's disease with invasive malignancy also showed p21 reactivity, whereas those without invasive malignancy did not. The authors claim that p21 reactivity could provide an additional prognostic index in cases of extramammary Paget's disease.[85]

Flow cytometric studies find 50–64% of cases of EMP to be diploid. Aneuploidy has been found to be associated with aggressive biological behaviour (recurrence, stromal and lymphatic invasion, and metastasis).[80]

Conclusions

Mammary and extramammary Paget's disease are uncommon intraepithelial adenocarcinomas. Both conditions have similar clinical features, which mimic inflammatory and infective skin diseases. Delay in clinical suspicion and hence in biopsy of suspicious lesions is therefore not uncommon. Histological diagnostic confusion can arise between Paget's disease and other neoplastic conditions affecting the skin, with the most common differentials being malignant melanoma and atypical squamous disease. The glandular differentiation of both mammary and extramammary Paget's disease is indicated by morphological appearances, the presence of intracellular mucin in many cases, and positive immunohistochemical staining for glandular cytokeratins, EMA, and CEA. The combination of careful assessment of morphological features with appropriate histochemical stains allows positive diagnosis in most cases in clinical practice.

Immunophenotypic heterogeneity between mammary and extramammary Paget's disease and within the subgroup of extramammary Paget's disease supports the prevailing hypothesis for the existence of primary and secondary versions, particularly of extramammary Paget's disease. It is generally accepted that most cases of mammary Paget's disease result from epidermotropic spread from intramammary neoplastic disease. The spectrum of antigen expression in cases of extramammary Paget's disease, with and without underlying carcinoma, provides support for the view that most cases show an intraepidermal origin, with a small proportion having an epidermotropic origin from an associated in situ or invasive neoplasm in an organ with contiguous epithelium.

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