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. (J Clin Pathol 2000;53:742–749)

Keywords: mammary Paget’s disease; extramammary Paget’s disease

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 confined to sweat gland ducts, and might be related to the apocrine glands. 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).3–5 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;6–8 (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,
with time, progress from intraepidermal neoplasm (in situ disease) to dermally invasive adenocarcinoma (in a fashion analogous to invasive malignant melanoma arising from superficial spreading malignant melanoma). This might subsequently metastasise to local lymph nodes and distant sites. Therefore, invasive carcinoma resulting from dermal invasion of epidermal Paget’s cells after a primary adenocarcinoma, which had given rise secondarily to extramammary Paget’s disease. 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. 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.

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. 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. 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). 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. 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. 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.

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. 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). Conservative surgery (excision of the nipple/areola complex) with adjuvant radiotherapy may be possible in selected cases. 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.

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.

**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. 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 insti-
gated. Extramammary Paget’s disease is an uncom-
mon neoplasm, which although it occurs most com-
monly in the anogenital region, can arise in any 
area of skin or mucosa. This disease arises 
moving 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.34 Extramam-
mary Paget’s disease of the external male and 
female genitalia may be associated with neo-
plasms 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.35 36

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.37 38 
In cases where there is a promi-
nent dermal invasive component, it may be 
possible to prove the primary site of origin of 
the tumour. A new variant of “mammary like” 
cutaneous glands, which combines morpho-
logical features of mammary, eccrine, and apo-
crine 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.39 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 endome-
trial, 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, hepato-
telial carcinoma, and renal cell carcinoma.36 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 coinciden-
tial 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 expres-
sion 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 extramam-
mary Paget’s disease, 70–80% of cases of peri-
anal disease arise secondary to invasive malig-
nancy 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.30 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 vapori-
sation. In patients unfit for radical surgery, radio-
therapy 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 dem-
onstrated histologically that the disease extends 
beyond the visible lesion—for example, pri-
mary vulval extramammary Paget’s disease can 
spread into urethral, upper vaginal, and 
cervical epithelia.43–45 Multiple surgical exci-
sions 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.14 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 46 48

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.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.7 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

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 keratogenous 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.52 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.64.65

SUPERFICIAL SPREADING MALIGNANT MELANOMA/LENTIGO MALIGNA AND PAGET’S DISEASE

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. Acaninar 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.64 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.65 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 DISEASE66 67

Toker cells are intraepidermal cells seen in 10% of normal nipples, which have also been described in fibropathelial 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. Irrespective of 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 epi-
dermis or hair follicle epithelium. It has been
found to be a sensitive, although not specific,
marker for mammary and extramammary
Paget’s disease.9 10 A small number of cases do
not label with anti-CK7, commonly those with
an underlying malignancy in an internal
organ.91 0 Anti-CK7 also marks some Toker
cells and Merkel cells so morphological assess-
ment of the labelled cells is necessary.16

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 66 72 73 However, GCDFP-15 ex-
pression 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 neo-
plasms. 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 anti-
bodies to HMFG are said to show greater epi-
thelial specificity than those to EMA.74

CARCINOEMBRYONIC ANTIGEN
Carcinoembryonic antigen (CEA) is a glyco-
protein normally detected in fetal epithelial
cells but which is also strongly expressed in
adenocarcinomas, particularly of the gastro-
intestinal 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.36 60 69

OSTEOSTERONE AND PROGESTERONE RECEPTORS
In mammary Paget’s disease, tumour cells gen-
erally 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 ex-
tramammary 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 cor-
relate with the presence of lymph node metas-
tases. 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. Mono-
clonal 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 com-
monly 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 oncprotein expression and epider-
mitropic spread, but might also reflect the fact
that most cases of mammary Paget’s disease are
associated with higher grades of ductal carci-
noma 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.75 80

S100 AND HMB-45
S100 is an acidic calcium binding protein
present in glial cells, Schwann cells, melano-
cyes, chondrocytes, adipocytes, and myoepi-
thelial cells. It is useful in the differentiation
between Paget’s disease and melanoma. How-
ever, 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.84
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 multi-
ple 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 con-
cluded 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 skin 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.\(^5\) p53 expression does not appear to have prognostic relevance in Paget's disease.\(^4\) 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.\(^8\)

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.

Mammary and extramammary Paget's disease


Mammary and extramammary Paget's disease

J Lloyd and A M Flanagan

J Clin Pathol 2000 53: 742-749
doi: 10.1136/jcp.53.10.742

Updated information and services can be found at:
http://jcp.bmj.com/content/53/10/742

These include:

References
This article cites 75 articles, 1 of which you can access for free at:
http://jcp.bmj.com/content/53/10/742#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Breast cancer (506)
Cancer: dermatological (106)
Dermatology (222)
Immunology (including allergy) (1664)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/