

Review

An overview of the pale and clear cells of the nipple epidermis

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Summary. The stratified squamous epithelium of the nipple-areola complex may contain pale or clear cells including: Paget's disease cells (PDCs), Toker cells (TCs), and so-called clear cells (CCs). Paget's disease is an uncommon presentation of breast carcinoma. PDCs are large, atypical, have abundant, pale-staining cytoplasm that may contain mucin secretion vacuoles and bulky heterochromatic nuclei. They are commonly concentrated along the basal layer and stain for EMA, CAM5.2, cytokeratin 7, and HER2/neu oncoprotein. TCs are bland cells with roundish and scant chromatin nuclei. They are found incidentally and are reactive for EMA, CAM5.2, and cytokeratin 7, but show negativity for HER2/neu oncoprotein. So-called CCs show varied morphology, are found incidentally, and have been variably interpreted by different authors. The majority of cells that have been called epidermal CCs fit the features of pagetoid dyskeratosis. These cells are reactive for high molecular weight cytokeratin. Other CCs showing signet-ring morphology present negativity for mucins and correspond to a fixation artefact.

Key words: Nipple, Pagetoid dyskeratosis, Paget's disease, Toker cells, Clear cells, Signet-ring cells, Breast carcinoma, Immunohistochemistry

Introduction

The nipple-areolar complex forms a disc of mammary skin showing increased melanin pigmentation. The nipple is centrally placed surrounded by the areola, and variably elevated above it. In the tip of the nipple there are 15-20 orifices which lead into the collecting ducts and lactiferous sinuses which deliver milk to the

exterior. In the non-lactating breast these duct openings are usually filled with plugs of keratin. The nipple and areola are covered by keratinizing stratified squamous epithelium similar to that seen in the epidermis elsewhere in the body. The collecting ducts show a double epithelial and myoepithelial lining. The epithelium is columnar and the myoepithelial cells lie between the epithelial layer and the basal lamina. A cross section of the major ducts shows an irregular, pleated or serrated outline and an investment with muscular tissue. The areola dermis contains numerous sebaceous glands. Some of them open directly onto the surface, whereas others drain into a collecting duct or share a common ostium with a lactiferous duct.

Diverse types of pale or clear cells are reported in the epidermis of the nipple-areolar complex. Most common cells include the following: (1) Paget's disease cells; (2) Toker cells; and (3) so-called epidermal clear cells or epidermal clear cell change, terms which have been used and made popular by numerous authors (Page and Anderson, 1987; Rosen and Oberman, 1993; Rosen, 1997; Tavassoli, 1999; Manavi et al., 2002; Bane et al., 2007; Li and Urmacher, 2007; Collins and Schnitt, 2007; Rosen, 2009). These clear keratinocytes have been analyzed and subjected to a thorough study by our group (Garijo et al., 2008).

In this review, we briefly summarize the main features of the pale and clear cells of the epidermis of the nipple with special reference to the so-called epidermal clear cells and their differential diagnosis.

Paget's disease cells

Alfred Velpeau (1854) was the first acknowledged author to write on an intriguing crusting lesion, located on the nipple of two patients, that now bears the name of Paget's disease. However, the distinguished French surgeon did not follow-up his patients and he did not establish any relationship between the nipple lesion and the development of breast carcinoma. Sir James Paget

(Paget, 1874) reported an eruption on the nipple and areola, with features of “ordinary chronic eczema” or “psoriasis,” that was followed by cancer of the breast within at the most two years. The superficial lesion of the nipple induced the underlying mammary cancer. However, Paget did not describe the histopathology of the disease, so the use of the term Paget’s cells for describing the malignant cells of the nipple epidermis is inappropriate.

George Thin (1881) who had early recourse to microscopy, is credited to be the first in illustrating the malignant cells of the nipple epidermis after studying four specimens exhibited in the pathological museum of the British Medical Association at Cambridge. Thin suggested that the disease should be called “malignant papillary dermatitis of the nipple” and concluded that the malignant dermatitis had neither the symptoms nor the pathological anatomy of any known skin disease. He believed that the secretions emerging from the mammary ducts injured the epidermis and that this process induced the underlying carcinoma (Thin, 1881). The concept that Paget’s disease represents the spread of carcinoma cells into the epidermis from an underlying breast carcinoma, through the duct system, was first advanced in 1904 by the Stockholm internist Jacobaeus (Jacobaeus, 1904) based on histological study of three cases. Muir (1927) confirmed these observations and also described the Paget’s disease secondary to an infiltrating primary carcinoma of the breast extending directly into the epidermis and accompanied by the intraepidermal spread of the malignant cells (Fig. 1A).

Paget’s disease is an uncommon presentation of breast carcinoma that accounts for 1-4.3% of all breast carcinomas (Bane et al., 2007). The disease can be observed in 1 of 3 ways: (a) in conjunction with an underlying ductal carcinoma in situ (DCIS), (b) in conjunction with an underlying invasive carcinoma, or (c) alone without any underlying carcinoma. The tumor is usually centrally located, within 2 cm of the areola, but occasionally can be more peripherally sited. In our series, the mean age of the patients was 61 years (range, 38 to 84 years). Clinically, the lesion is centred on the nipple and may extend to the areola. In advanced cases the lesion involves the skin surrounding the areola. The nipple may appear normal, thickened, erythematous, eczematoid, hemorrhagic, pigmented, erosive, ulcerated, weeping or crusted. The lesion may be associated with pruritus, burning sensation, tingling or pain. Microscopically, cells invading epidermis are large, and they have abundant, pale-staining cytoplasm (Fig. 1B) that may contain mucin secretion vacuoles. Nuclei are bulky, atypical sometimes with prominent nucleoli (Fig. 1C). These cells occur singly, but more commonly form clusters in the basal portion of the epidermis and occasionally can replace large areas of the epidermis. In this latter situation Paget’s cells show solid or glandular structures (Shousha, 2007). Mitoses are usually present. Tumor cells adhere to one another poorly and may detach from one another resulting in cleft-like

acantholysis. The epidermis commonly exhibits hyperkeratosis and acanthosis. The underlying lactiferous ducts contain carcinoma cells cytologically similar to the cells invading the epidermis. The superficial dermis is usually infiltrated by a moderate-to-intense lymphocytic reaction.

An anaplastic form of Paget’s disease has been reported (Rayne and Santa Cruz, 1992). Pigmented mammary Paget’s disease is another form that must be differentiated from melanoma of the nipple (Requena et al., 2002; Mitchell et al., 2006). Local production of melanocytic chemotactic factor by neoplastic cells of the breast carcinoma when they reach the epidermis has been postulated as the cause of pigmentation. Another possibility is the phagocytosis or transfer of melanin from melanocytes (Requena et al., 2002).

The underlying carcinoma, *in situ* or infiltrating, is present in more than 95% of the cases and it is in most cases of ductal type. Intraductal carcinoma characteristically has a comedo or solid growth pattern. Very rarely, lobular intraepithelial neoplasia or infiltrating lobular carcinoma is encountered (Sahoo et al., 2002).

In the rare cases of Paget’s disease without an underlying carcinoma, it is suggested that the disease is a carcinoma *in situ* arising from intraepidermal duct cells (Toker cells) or from basal multipotential cells with capacity of glandular differentiation (Eusebi et al., 2003).

Special stains often, but not invariably, detect mucin in the cytoplasm of intraepidermal cells. PAS after diastase, Alcian blue, and mucicarmin may all be in use. Immunohistochemically, Paget’s disease cells show reactivity for epithelial membrana antigen (EMA), low molecular weight cytokeratin (LMWCK), cytokeratin 7 (CK7), carcinoembryonic antigen (CEA) polyclonal and HER2/neu oncoprotein (Fig. 1D), and they are negative for high molecular weight cytokeratin (HMWCK), estrogen receptor, progesterone receptor, HMB-45 and Melan-A (Garijo et al., 2008).

At present the origin of Paget’s disease cells is controversial although there is a widespread opinion that these cells result from an epidermotropic migration of neoplastic elements from an underlying ductal carcinoma. De Potter et al. (1994) concluded that Paget’s disease cells spread through the epidermis due to the motility induced by a chemotactic factor, which is released by epidermal keratinocytes and whose influence is mediated by the HER2/neu oncoprotein. The motility can be inhibited *in vitro* using monoclonal antibodies against the extracellular domain of the HER2/neu oncoprotein. However, Morandi et al. (2003) using methods of clonality (loss of heterozygosity and mitochondrial DNA displacement loop sequence analysis) and microdissection in 10 cases, demonstrated that in no fewer than 2 cases, Paget’s disease cells were genetically different from the underlying carcinoma. Therefore, these authors suggested that the rule of epidermotropism by neoplastic cells from an underlying

Pale and clear cells of the nipple epidermis

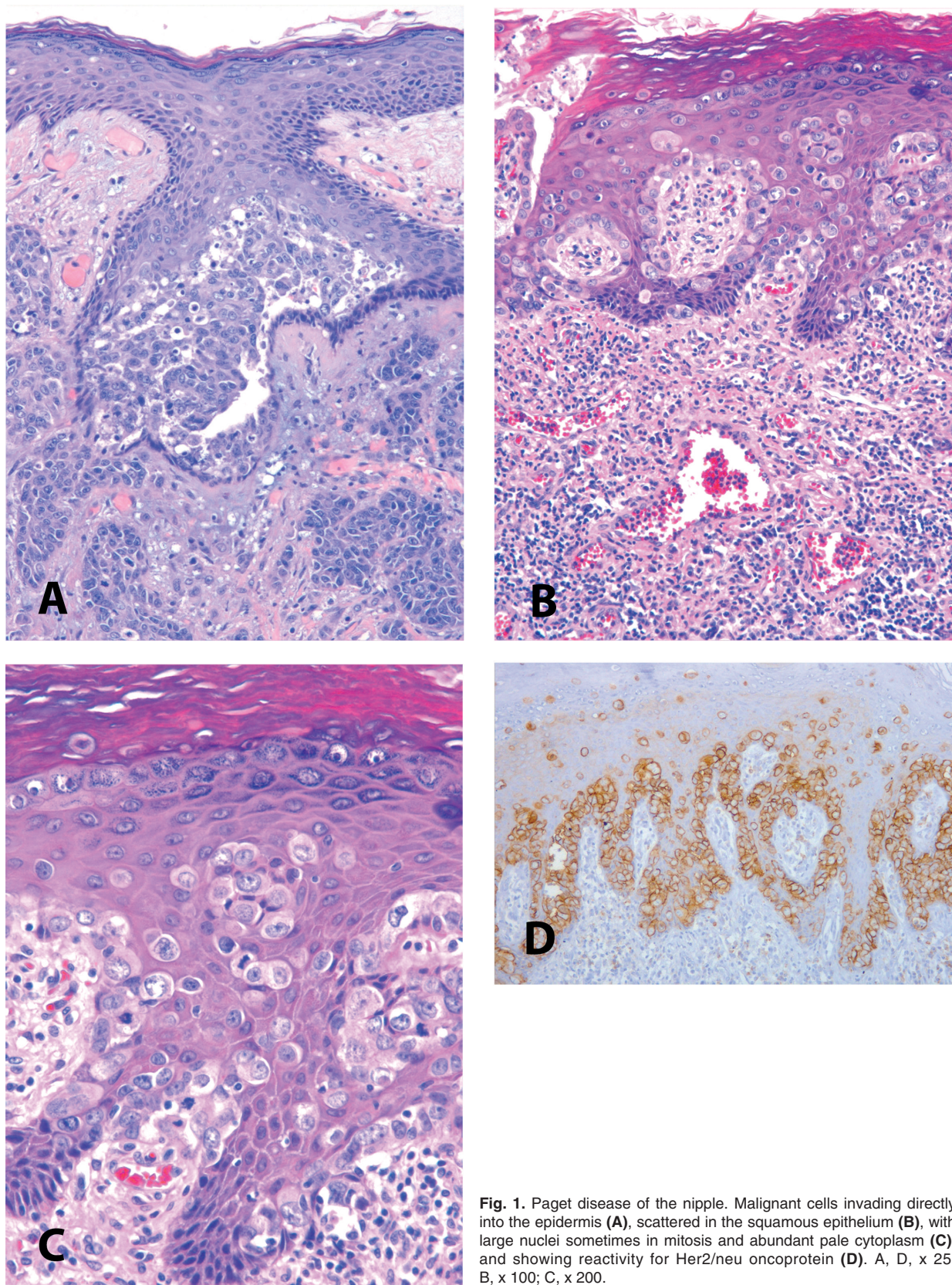


Fig. 1. Paget disease of the nipple. Malignant cells invading directly into the epidermis (**A**), scattered in the squamous epithelium (**B**), with large nuclei sometimes in mitosis and abundant pale cytoplasm (**C**), and showing reactivity for Her2/neu oncoprotein (**D**). A, D, x 25; B, x 100; C, x 200.

Pale and clear cells of the nipple epidermis

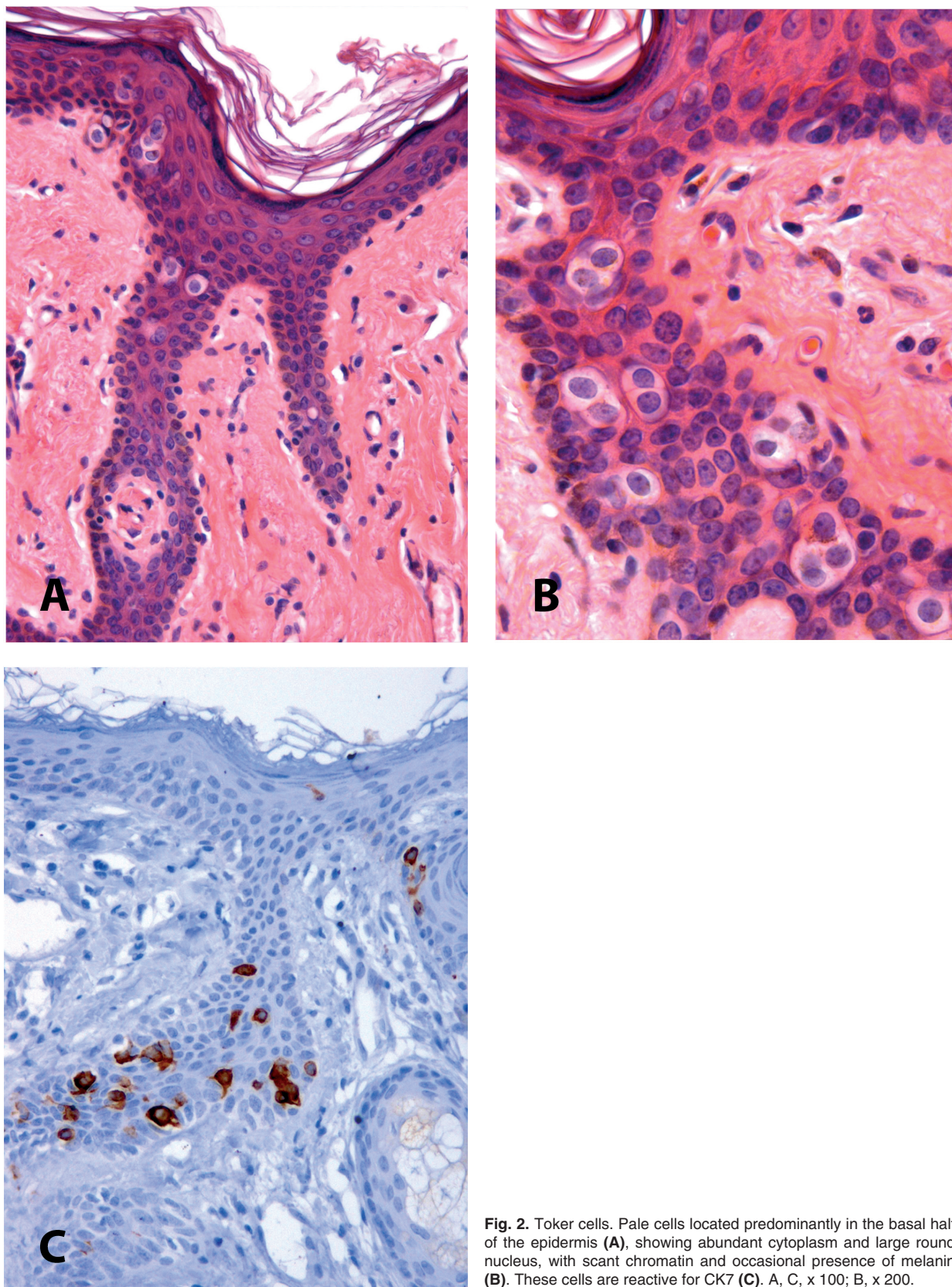


Fig. 2. Toker cells. Pale cells located predominantly in the basal half of the epidermis (**A**), showing abundant cytoplasm and large round nucleus, with scant chromatin and occasional presence of melanin (**B**). These cells are reactive for CK7 (**C**). A, C, x 100; B, x 200.

malignant lesion is not applicable to all cases. In a minority of cases (about 20%) Paget's disease cells might be the result of neoplastic transformation of pre-existing intraepidermal ductal nonneoplastic cells (Toker cells). Consequently, the underlying carcinoma should be, in these cases, a coincidental malignant tumor (or collision tumor). Thus, Paget's disease of the nipple is not a homogeneous disease.

Toker cells

Orr and Parish (1962) in a survey of 60 cases of Paget's disease from different origins, made mention briefly of clear cells resembling those seen in the disease. These cells were seen in the normal epidermis of the nipple, although in much smaller numbers. These authors illustrated the cells (their figure 5) but they did not elaborate further. On the other hand, the authors concluded that the cells of Paget's disease were not of neoplastic nature and suggested that they were degenerated melanocytes.

Cyril Toker (1970) in a seminal article published in

the journal *Cancer* accomplished a detailed description of pale cells in surface epithelium of the nipple that now bear his name. Toker detected these cells, by conventional microscopy, in 31 cases (9%) in the course of a study of 340 nipples of breasts that had been removed during radical mastectomy for breast carcinoma. In addition, this author examined 190 nipples removed from 101 unselected autopsy cases in an entirely random fashion, and without any regard to age, sex, or cause of death. Pale cells were noted in 23 nipples (12%) removed from 18 patients (Toker, 1970).

Toker was able to make the following observations: (a) the nipples themselves were devoid of gross abnormality; (b) the pale cells were present both in males and females, the ages of whom ranged from 26 to 76 years; (c) detection of the cells upon material prepared in a routine fashion with hematoxylin and eosin could be made only in about 10% of cases; (d) the cells referred to were smaller in size than typical cells of Paget's disease and larger than their squamous neighbors (Fig. 2A). They were polygonal or oval in shape. Their nuclei were roundish and exhibited moderate quantities

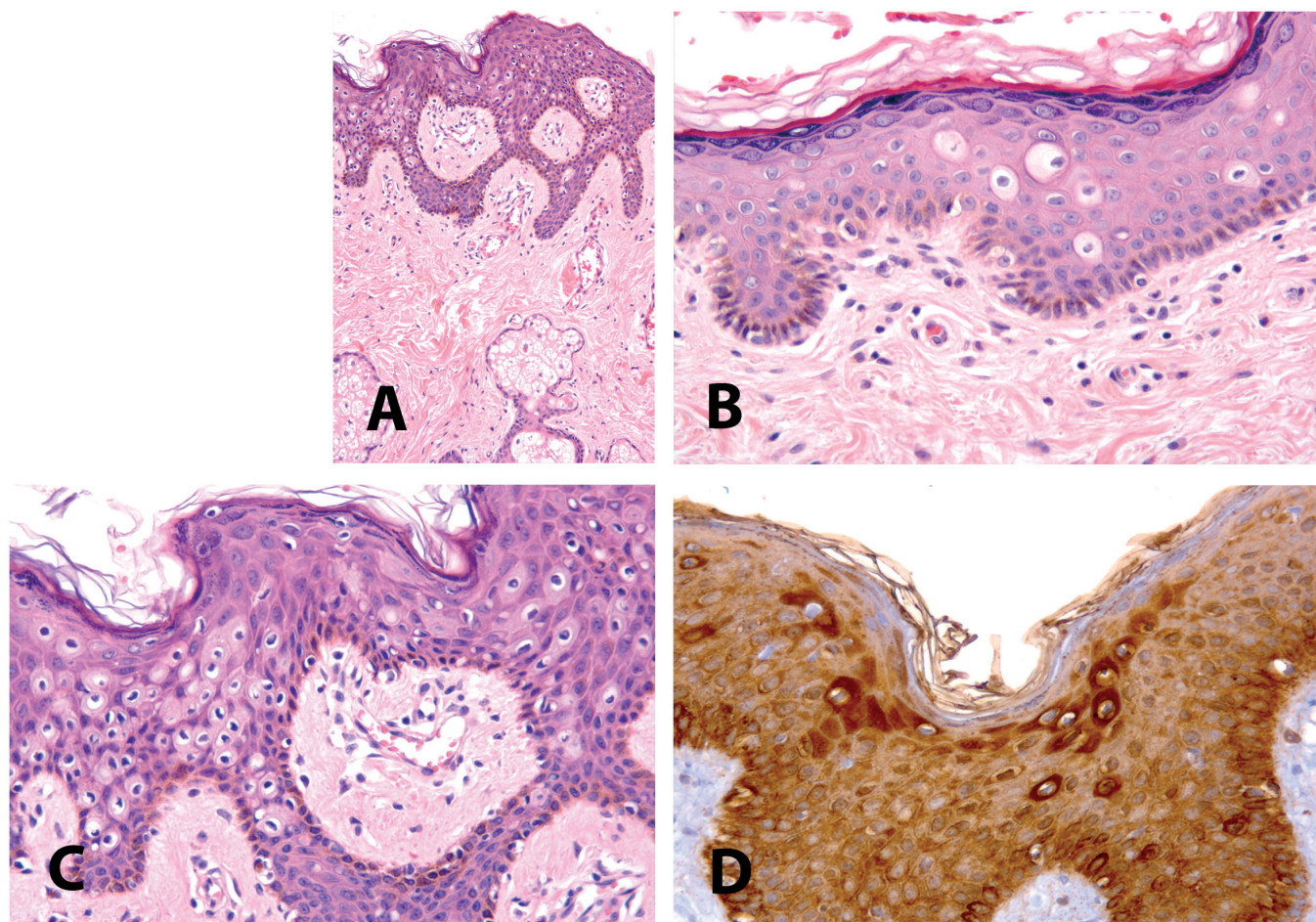


Fig. 3. Pagetoid dyskeratosis. The cells are large and pale arranged in clusters (A) or scattered as single elements (B). Each cell shows a condensed nucleus and a perinuclear halo (C). These cells display reactivity for HMWCK (D). A, x 16; B, D, x 200; C, x 100.

of chromatin content with clarity of the nuclear substance. Nucleoli were prominent in many cases, inconspicuous in others. Mitoses were infrequent. Their cytoplasm was often abundant and pale, yet lacking complete clarity. The cells were rather monomorphous and concentrated in greatest number within the basal layer of the epidermis. They were organized in small groups (Fig. 2B) or scattered solitary elements. At times, the cellular aggregates formed small tubules, each lined by a single layer of cells surrounding a small central lumen; (e) no significant inflammatory infiltrate was present in the dermis.

Toker cells are usually found around the openings of the lactiferous ducts. Occasional cytoplasmic melanin can be observed. This feature suggests that these cells may phagocytose the pigment from epidermal melanocytes, similarly to what occurs with epidermal keratinocytes.

In our own series we detected Toker cells by conventional microscopy in 8.3% of the nipples of breasts that had been removed during simple or radical mastectomy. These cells are difficult to identify upon material prepared in a routine fashion and some authors find them with less frequency than 10% (Rosai, 2004). However, the use of keratin 7 antibody raised the incidence of Toker cells to 83% in a series of 18 non neoplastic post-mortem cases (Lundquist et al., 1999), albeit often in pathetically small numbers, and to 65% in a retrospective study of 20 cases of accessory nipples (Willman et al., 2003).

Toker cells can coexist with Paget's disease cells and may even show notable hyperplasia (van der Putte et al., 1995). Toker cell hyperplasia has been also observed in a supernumerary nipple (Decaussin et al., 1998). Rarely, Toker cells can be numerous and atypical as to require a careful distinction from malignant cells of Paget's disease (Di Tommaso et al., 2008).

The immunohistochemical study confirms that Toker cells are epithelial and of lactiferous duct origin. They are positive for EMA, LMWCK, and CK7 (Fig. 2C). However, they show negativity for HER2/neu oncoprotein and polyclonal CEA. Therefore, this profile is different from that shown by Paget's disease cells (Garijo et al., 2008).

As Toker cells may assume a rather florid aspect and precipitate a diagnosis of Paget's disease, they must be taken into account in nipple biopsies to avoid misinterpretations.

Clear cells

Clear cells in surface epithelium of the nipple show varied morphology, are found incidentally, have been

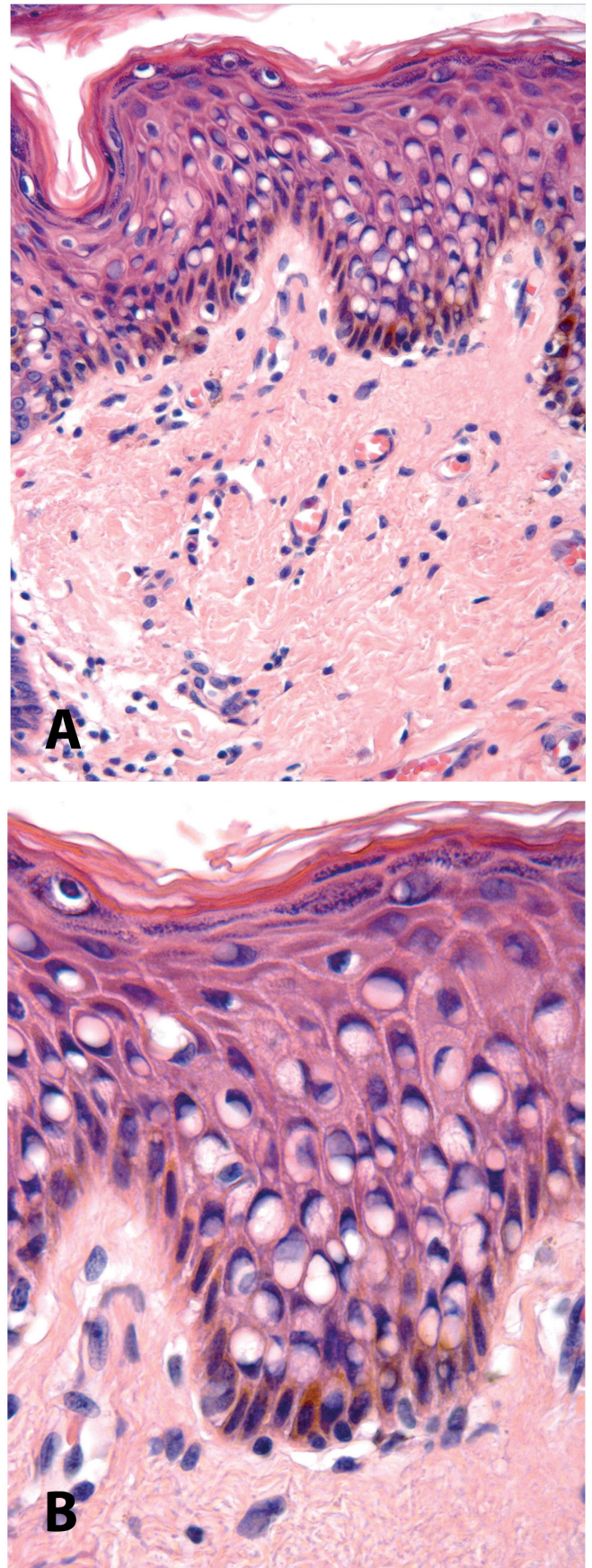


Fig. 4. Clear cells with signet-ring morphology. Abundant keratinocytes with marked vacuolization and eccentric nuclei (A). The large vacuoles are empty (B). A, x 100; B, x 400.

illustrated to differentiate from Paget's disease cells, and have been variably interpreted by different authors.

Rosen (Rosen, 1997, 2009) described two varieties of clear cell change in the epidermis: (a) type 1, cells provided with small inconspicuous nuclei with vacuolated cytoplasm; and (b) type 2, cells with marked vacuolization and eccentric nuclei resembling signet ring cells. Both types of cells constituted a non-neoplastic alteration of keratinocytes that tended to occur in isolated cells in the upper layers of the epidermis. Mucin and other secretory substances detectable in Paget's disease cells were absent.

Type 1 cells were also illustrated by Page and Anderson (1987), Rosen and Oberman (1993), Suster (1996), and Li and Urmacher (2007). Furthermore, Suster (1996) and Li and Urmacher (2007) identified type 1 of clear cells as Toker cells. Type 2 cells were also illustrated by Tavassoli (1999), and by Collins and Schnitt (2007). These last authors pointed out that some of these cells were derived from epidermally located mammary ductal epithelium.

The routine study of the nipple during our practice of surgical pathology convinced us that nipples taken from mastectomy specimens exhibited an epidermal cellular population of clear cells that, in the majority of cases, fitted the features of pagetoid dyskeratosis cells. Therefore, we undertook a thorough study of the so-called clear cells of the nipple epidermis (Garijo et al., 2008).

In our opinion the term clear cells or clear cell change of the nipple epidermis encompasses two types of cells: (i) pagetoid dyskeratosis cells and (ii) clear cells with morphology of signet-ring cells.

Pagetoid dyskeratosis of the nipple epidermis.

Pagetoid dyskeratosis cells are defined as large keratinocytes showing a distinct cytoplasmic limit, with central, condensed pyknotic nuclei and a pale acidophilic cytoplasm with a clear perinuclear halo (Tschen et al., 1988; Val-Bernal and Garijo, 2000; Val-Bernal et al., 2000; Val-Bernal and Pinto, 2001; Garijo et al., 2001, 2008). Intercellular bridges between these clear cells and surrounding keratinocytes are evident. Most of the pagetoid dyskeratosis cells appear as single elements (Fig. 3A) scattered among the prickly cells. However, sometimes they can be seen forming clusters or nests, but they do not form glandular structures (Fig. 3B). These cells were considered an epidermal artefact (Mehregan, 1980; Civatte, 1984). Mehregan suggested that the appearance of these cells was most likely artefactual as a result of factors such as occlusion, with resulting moisture in the intertriginous areas or to other unknown factors. Civatte thought these pale epithelial cells were artefactual as a result of poor fixation, superficial intradermal injection of anesthetic solution with extension of local edema into the epidermis, or moisture, especially in intertriginous areas. Tschen et al (1988) believed these cells were probably a small part of

the normal population of keratinocytes and that, under certain circumstances, they can be induced to proliferate. Among the inductors, friction was the most probable.

We have studied extensively pagetoid dyskeratosis cells in diverse locations and we have described them for first time in mucosas and in the nipple (Val-Bernal and Garijo, 2000; Val-Bernal et al., 2000; Val-Bernal and Pinto, 2001; Garijo et al., 2001, 2008).

According to our experience, most of the so-called epidermal clear cells in the nipple epidermis correspond to pagetoid dyskeratosis cells. In a study of 288 mastectomy specimens these cells were found in 184 cases (64%), and they were a prominent finding in 37 cases (13%). Pagetoid dyskeratosis cells are an incidental finding owing to premature keratinisation that is different from other forms of dyskeratosis. Thus, these cells mature into orthokeratotic squamulae and no acantholysis or parakeratosis results from it.

In the setting of normal and pathologic nipple, pagetoid dyskeratosis may appear as the nipples are susceptible to trauma as a result of their protrusion, and to friction or rubbing from contact with surrounding structures. Furthermore, Piqué-Durán et al. (2006) observed that pagetoid dyskeratosis was most frequently seen in soft fibroma than in acrochordon. The former lesion is larger and more susceptible to trauma or friction.

In cases in which pagetoid dyskeratosis is conspicuous (Fig. 3C) there is a hazard of overdiagnosis of the patient's disease. Routine histological examination is usually sufficient to distinguish the characteristic appearance of these cells. However, pagetoid dyskeratosis cells show a distinctive immunohistochemical profile as they reveal strong reactivity for high-molecular weight cytokeratin or 34betaE12 (Fig. 3D) and negativity for LMWCK, CK7, EMA, polyclonal CEA, and HER2/neu oncoprotein, all these in contrast to Paget's disease cells, Toker cells, and surrounding keratinocytes. These keratinocytes show much weaker reactivity for HMWCK (Garijo et al., 2008).

Clear cells with signet-ring morphology in the nipple epidermis

Clear cells with marked vacuolization and eccentric nuclei resembling signet-ring cells (Fig. 4A) have been described within the group of clear cells of the nipple epidermis (Rosen, 1997, 2009; Tavassoli, 1999; Collins and Schnitt, 2007). This change is not rare in the mid epidermis and tends to occur in isolated cells. However, it is uncommon to see this alteration affect a large number of epidermal cells. In our series this prominent change occurred in 0.7% of the cases. The cells show large vacuoles (Fig. 4B) negative for periodic-acid Schiff (PAS), diastase digestion-PAS, Alcian blue, mucicarmine and colloidal iron. These vacuoles are empty and the rest of the cytoplasm shows the reactivity of the keratinocytes.

In spite of the fact that authoritative books (Rosen, 1997, 2009; Tavassoli, 1999; Collins and Schnitt, 2007) and prestigious authors (van der Putte et al., 1995; Manavi et al., 2002) consider these cells real or genuine keratinocytes, we believe they are artefacts due to formalin fixation.

Mehregan and Pinkus (1966) and Pinkus and Mehregan (1969) in a report on artefacts in dermatopathology described epidermal cells with signet-ring morphology which were attributed to the specimen freezing during fixation. The vacuolization was imputed to intracellular formation of ice crystals. However, this freezing artefact occurred only in the specimens fixed in formalin solution. Luna (1968) similarly included this type of vacuolization, of epidermal cells, among formalin fixation artefacts due to temperature below freezing point. However, these vacuoles are of roundish or elliptical morphology, not showing a polygonal profile.

On the other hand, artefactual signet-ring-like cells have been described in other tissues, such as gastrointestinal mucosa (Wu et al., 2001), malignant lymphomas (Perrone et al., 1986; Arista-Nasr et al., 1997) lymphocytes and stromal cells in prostate transurethral resections (Alguacil-García, 1986) or prostatic needle biopsies (Schned, 1987), stromal nodule in simple prostatectomy (Wang and Humphrey, 2002) and extragastrointestinal stromal tumors (Weiss and Goldblum, 2008). All cases reported with this type of artefact were fixed in formalin. Ultrastructural studies showed cells with crescentic nuclei, scant granular cytoplasmic material surrounded the nucleus and a large clear empty space with no vacuolar or cell membranes (Alguacil-García, 1986).

This disturbing artefact caused by formalin fixation in the nipple may induce confusion with squamous signet ring-cell carcinoma (McKinley et al., 1998), particularly when it is a prominent histologic finding. Characteristic morphology showing pycnotic, homogeneous, crescentic, structureless nuclei and histochemical and immunohistochemical studies permit the correct diagnosis excluding other types of cells.

Differential diagnosis of the pale and clear cells of the nipple epidermis

The term Pagetoid pattern of epidermal involvement entails a wide category of lesions that include all discrete non-Malpighian or abnormal Malpighian intraepidermal cells occurring singly or in nests in the epidermis. Cells which can show Pagetoid spread are of epithelial, melanocytic, neuroendocrine, lymphoid and histiocytic differentiation (Kohler et al., 1998).

Routine histologic examination is usually enough to distinguish the characteristic features of the cells involving the nipple epidermis and permits differentiation of other entities with epidermal pale cells, such as: clear cell Bowen disease or Pagetoid squamous cell carcinoma in situ (Suster, 1996; Williamson et al.,

2000), superficial spreading malignant melanoma or Pagetoid melanoma in situ or infiltrating (Papachristou et al., 1979; Clark et al., 1986; Glasgow et al., 1987; D'Aiuto et al., 1991; Kinoshita et al., 2007), clear cell papulosis (Kuo et al., 1987; Lee and Chao, 1998; Gianotti et al., 2001; Kim et al., 2002; Mohanty et al., 2002; Kumarasinghe et al., 2004; Benouni et al., 2007), koilocytosis (warts), and glycogen rich cells. As the pattern can be quite similar, in some cases correct diagnosis requires clinical correlation, histochemical study and immunophenotyping of the intraepidermal cells.

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