

Original Article

Mammary Paget's disease: Evidence of diverse origin of the disease with a subgroup of Paget's disease developing from the superficial portion of lactiferous duct and a discontinuous pattern of tumor spread

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The pattern of spread of intraductal carcinoma associated with mammary Paget's disease has not been well studied. The purpose of this study was to examine the site of origin and the pattern of tumor spread with a three-dimensional view by serial sectioning of the tissue blocks from 19 cases of Paget's disease. Intraductal carcinoma in the superficial portion of the lactiferous ducts was seen in continuity with the overlying epidermis with Paget's disease in all 19 cases. In seven cases that had adequate tissue sampling, five showed a continuous pattern of the intraductal carcinoma within the superficial as well as the deep breast tissue. In the remaining two cases, a portion of benign duct was identified between the intraductal carcinoma in the superficial lactiferous duct and the deep breast tissue. This discontinuous pattern of spread of the intraductal carcinoma was also identified in the foci of carcinoma in deep tissue. In the five cases in which the tumor involved the skin and only the superficial portions of the lactiferous duct, the leading edge of the intraductal carcinoma was seen orientated in the direction of the nipple towards the deep breast tissue. Our study of Paget's disease demonstrated that in addition to tumor spread along the lactiferous ducts from intraductal carcinoma in the deep tissue towards the nipple, there was a group of Paget's disease arising from the nipple. These lesions included: (i) lesions limited to the areolar tissue; and (ii) lesions with intraductal carcinoma involving the duct system in both superficial and deep breast tissue with and, possibly, without skip areas pattern of spread. Although certain cases of Paget's disease may appear superficial, an independent associated carcinoma in deep breast tissue has to be ruled out.

Key words: ductal carcinoma *in situ*, lactiferous duct, mammary Paget, nipple, tumor spread

Paget's disease of the nipple is characterized by the presence of neoplastic cells in the epidermis which have the same cytological appearance and immunohistochemical and oncogenic expression as the malignant cells of an underlying intraductal carcinoma.^{1–3} Many histopathological and immunohistochemical features of mammary Paget's cells are similar to those seen in extra-mammary Paget's cells.^{4–10} One of the exceptions is Her-2/neu oncogen expression which is present in the majority of cases of mammary Paget's disease, and not identified in extra-mammary disease.^{11–13} Since Her-2/neu-positive breast carcinoma only represent a subset of breast carcinoma, this oncogenic expression is probably specific to the type of tumor. Despite many similarities, the pathogenesis of mammary Paget's disease is considered to differ from that of the extra-mammary sites. In the latter sites, the neoplastic cells arise from the epidermis, whereas those of the nipple are commonly believed to develop as a result of secondary spread due to the extension or migration of malignant cells from an underlying breast carcinoma.^{7,14,15} In this study, we reviewed the topographic and histopathological features of mammary Paget's disease with special attention to the site of origin of the disease and the pattern and direction of tumor spread from the original site.

MATERIALS AND METHODS

Thirty cases of mammary Paget's disease were retrieved from the surgical pathology files at The Ottawa Hospital, Civic Campus. For the purpose of simplification of the study, 11 cases associated with invasive carcinoma were excluded from the study. Ten cases of mastectomy for breast carcinoma with extensive intraductal carcinoma were used as controls. For each case of Paget's disease, tissue blocks were obtained by sectioning the nipple in a plane perpendicular to the skin surface. Coronal sections (parallel to the skin

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surface) were also obtained in six cases. For all control cases, serial coronal sections were made. Serial sectioning (20–200 sections) to establish a three-dimensional view was performed for tissue (1–2 blocks for each case) in cases with ducts containing the intraductal carcinoma without a readily identified connection with the overlying epidermis (35 blocks for 25 cases). Similar serial sectioning was also performed for cases with adequate tissue sampling of the intraductal carcinoma in the nipple and deep breast tissue (11 blocks for four cases). Sections of formalin-fixed paraffin-embedded tissue, 4 μ m were stained with hematoxylin-phloxine-saffron (HPS). The size of each lesion was measured on the slides with the diameter recorded as the greatest dimension of the skin involved by the tumor cells. The depth was recorded as the greatest length of duct containing intraductal carcinoma or the distance from the nipple skin to the deep margin of the invasive carcinoma. Separate foci of intraductal carcinoma in the same duct system were defined as foci of carcinoma separated by benign ducts without significant epithelial hyperplasia more than 1 mm in length.

RESULTS

Table 1 outlines the pathological features and clinical follow up of the 19 study cases. We arbitrarily divided the cases into superficial lesions involving only the superficial portions of the duct (1.5 cm or less in depth) and deep lesions involving the entire length of a long portion of the duct, extending from the epidermis to the deeper breast tissue (more than 1.5 cm in depth).

In addition to the findings presented in Table 1, there were other important observations. The intraductal carcinoma was usually of high nuclear grade and of comedo or solid type. Ducts with intraductal carcinoma and ducts with pagetoid spread were grouped adjacent to each other (Figs 1a,b, 2a,b, 3). The entire superficial portion of lactiferous ducts could be visualized with a two-dimensional microscopic view (four cases) and a three-dimensional microscopic view (15 cases). It became apparent that all intraductal carcinomas that had an identifiable connection with the skin were seen in continuity with epidermis affected by Paget's disease.

Table 1 Pathological and clinical follow up

Groups of lesion	No. cases	Depth in cm (mean)	Diameter in cm (mean)
<i>Superficial lesions:</i>			
Continuous ductal spread	5	0.3–1.5 (0.8)	1–2 (1.5)
Associated with a separate area of carcinoma in deep tissue (skip area between superficial and deep carcinomas)	1 ^a	1	1
<i>Deep lesions</i> ^b :			
Total	13	1.5–4 (2.9)	0.1–1.5 (1.0)
	19	0.3–4 (2.2)	0.5–1.5 (1.1)

^a The cross-sections of the nipple at the base contained no intraductal carcinoma. The areas of carcinoma in the deep breast tissue were in the direction of the longest lactiferous ducts having intraductal carcinoma. ^b A three-dimensional microscopic view of the entire ducts with intraductal carcinoma from the nipple was available in four cases, one case had skip areas (more details in the text) and one case was associated with an invasive lobular carcinoma in the contralateral breast.

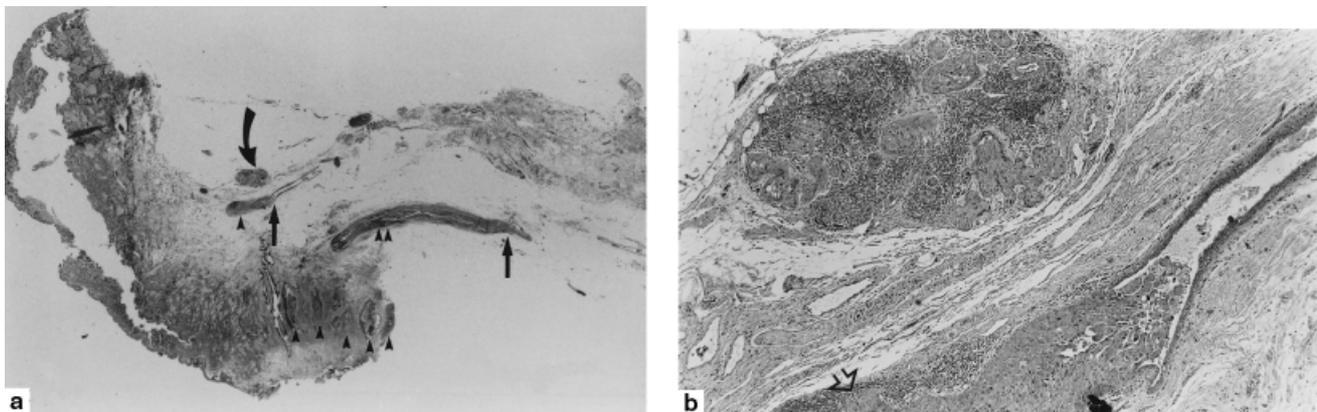


Figure 1 A superficial type lesion of Paget's disease involving only the proximal lactiferous ducts and not associated with invasive duct carcinoma. (a) Low magnification showing the intraductal carcinoma involving several lactiferous ducts (arrowheads). Note the leading edge of the intraductal carcinoma (arrows), the longest duct (double arrowhead) with the intraductal carcinoma confirmed by the serial sections and multiple sections of the nipple, and a small lobule with cancerization (curved arrow). (b) High magnification showing a lactiferous duct with intraductal carcinoma having the leading edge in the direction from nipple to the deep breast tissue and having a collateral branching duct with intraductal carcinoma (arrow) extending into a lobule (curved arrow in Fig. 1a).

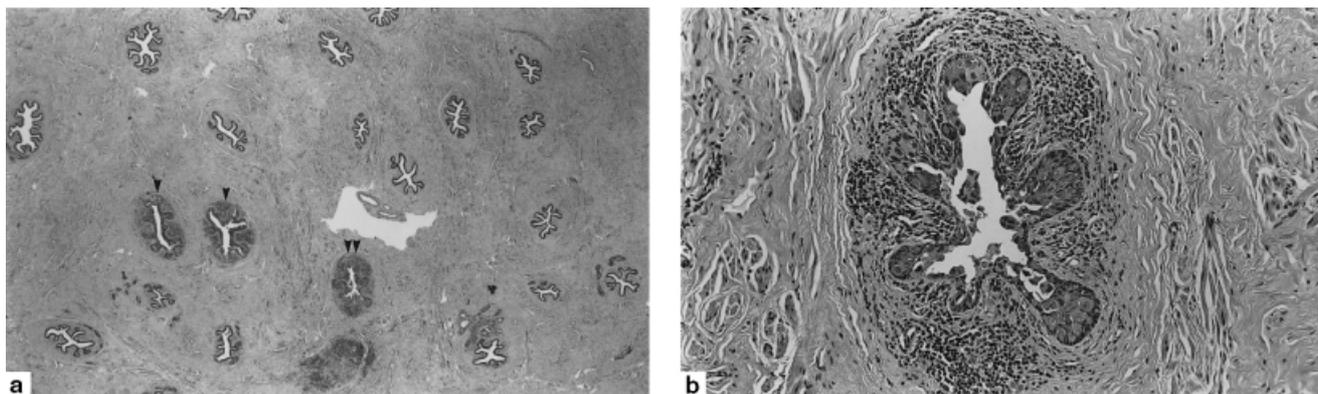


Figure 2 (a) Cross-section at the base of the nipple of another case of Paget's disease showing the presence of intraductal carcinoma in three ducts (arrowheads). (b) High magnification of a duct with intraductal carcinoma indicated by the double arrowhead in Fig. 2a.

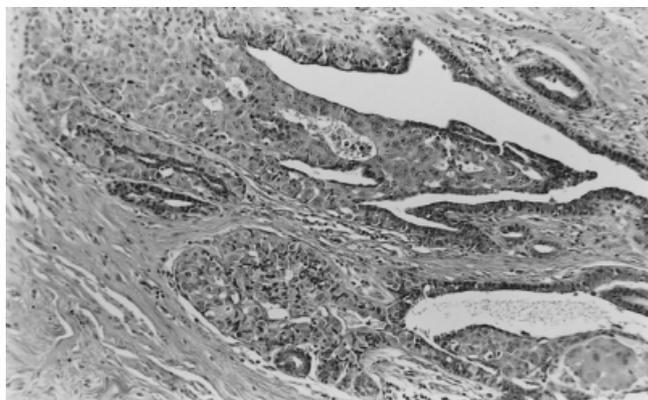


Figure 3 Pagetoid spread in the direction of nipple towards the deep breast tissue along the lactiferous ducts.

In the group of superficial lesions, the leading edges of the intraductal carcinoma (junction between the intraductal carcinoma or ducts with pagetoid spread and the benign ducts or acini) of the superficial lesion were identified (Figs 1a,b, 3). These edges were orientated from the nipple towards the deep breast tissue. One case in this group had a separate focus of intraductal carcinoma in the deep breast. The cross-sections of the nipple at the base in this case contained no intraductal carcinoma (foci of intraductal carcinoma separated by a portion of non-neoplastic duct more than 3 mm in length) (Fig. 4a–e). The area of intraductal carcinoma in the deep breast tissue was located in the territory related to the longest lactiferous duct having the intraductal carcinoma in the nipple.

In the group of deep lesions, one case was associated with a focus of invasive lobular carcinoma in the contralateral breast. In another four cases, serial sections of the entire duct with intraductal carcinoma were available and a three-dimensional view of the duct structure and collateral branches were studied. In these cases, intraductal carcinoma

showed continuous spread involving the entire length of the longest duct (connected to an area of epidermis with Paget's disease) leading to the areas of carcinoma in the deep tissue. In one of these four cases, intraductal carcinoma in the deep tissue showed focal areas having a discontinuous pattern of tumor spread (Fig. 5a–c). For the other cases, breast tissue sampling was not adequate to identify the existence of a connection between the superficial and deep lesions. However, in three cases in which the orientation of the sections was possible, the deep components of the lesion were located in the segment of the breast belonging to the longest duct containing the intraductal carcinoma.

In the group of 10 cases without mammary Paget's disease, the tumor consisted of an extensive intraductal carcinoma with and without invasive carcinoma in the deep breast tissue. The intraductal carcinoma was seen extending along lactiferous ducts up to a distance of 0.5 cm and 1 cm from the nipple epidermis, respectively, in two cases.

DISCUSSION

Based on the histopathological and immunohistochemical similarities between the Paget's cell and underlying intraductal carcinoma cells, it is commonly believed that in Paget's disease, the tumor spreads upwards along the duct, from the origin in the deep breast tissue into the nipple epidermis.^{7,14,15} In the present study, this pathogenic pathway of development of Paget's disease was supported by: (i) four cases in the group of deep lesions with demonstrable continuity of intraductal carcinoma in the deep breast tissue, superficial lactiferous ducts and nipple skin; and (ii) two of 10 cases without Paget's disease but with spread of the intraductal carcinoma to the areolar tissue.

In the five cases of the group of superficial lesions, there was only a minimal extent of underlying intraductal carcinoma. This type of Paget's disease has been previously

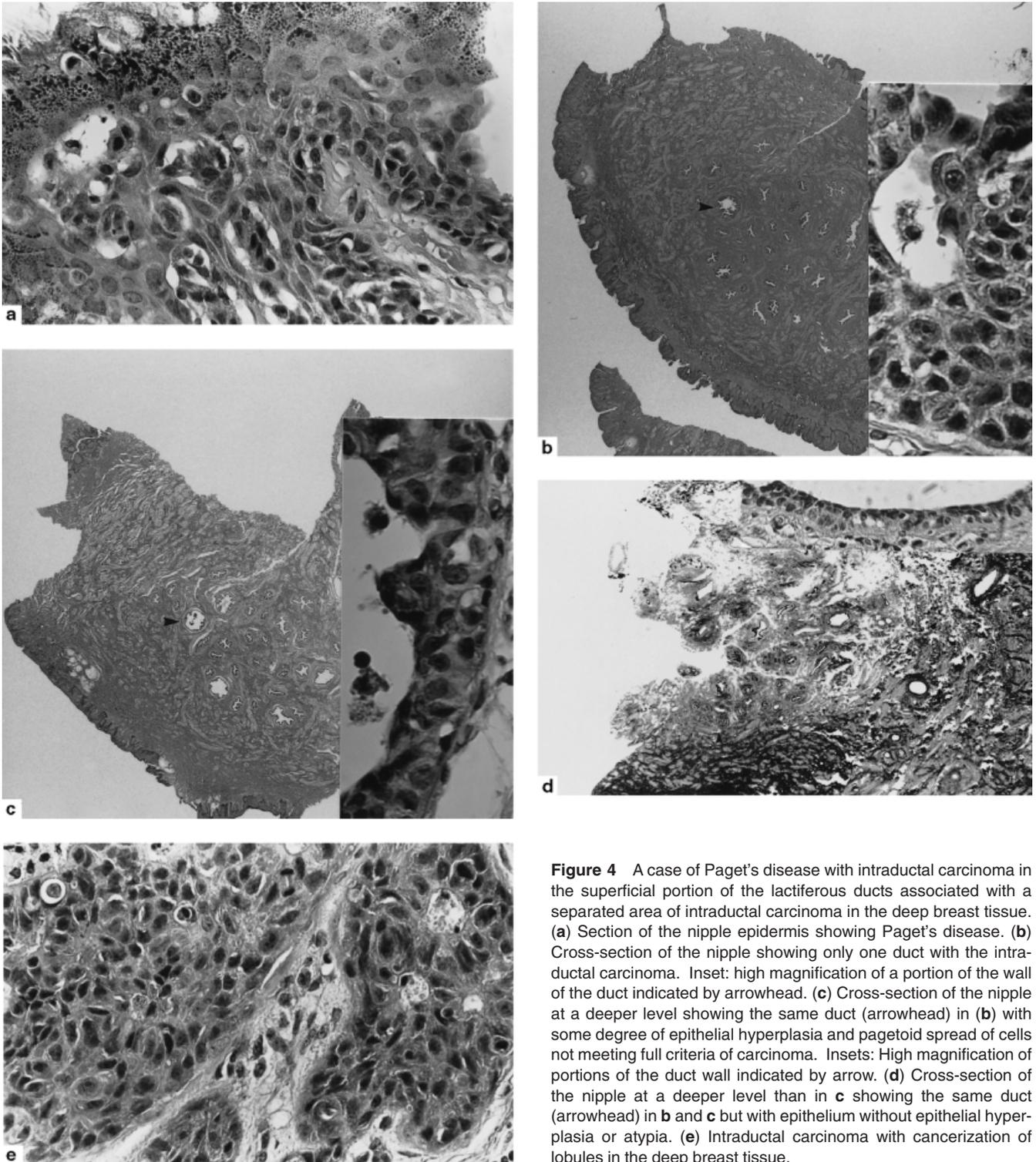


Figure 4 A case of Paget's disease with intraductal carcinoma in the superficial portion of the lactiferous ducts associated with a separated area of intraductal carcinoma in the deep breast tissue. (a) Section of the nipple epidermis showing Paget's disease. (b) Cross-section of the nipple showing only one duct with the intraductal carcinoma. Inset: high magnification of a portion of the wall of the duct indicated by arrowhead. (c) Cross-section of the nipple at a deeper level showing the same duct (arrowhead) in (b) with some degree of epithelial hyperplasia and pagetoid spread of cells not meeting full criteria of carcinoma. Insets: High magnification of portions of the duct wall indicated by arrow. (d) Cross-section of the nipple at a deeper level than in (c) showing the same duct (arrowhead) in (b) and (c) but with epithelium without epithelial hyperplasia or atypia. (e) Intraductal carcinoma with cancerization of lobules in the deep breast tissue.

reported.^{16,17} The topographic pattern of the intraductal carcinoma in these five cases suggests an origin of Paget's disease within the nipple. Possible sites include the superficial portion of the lactiferous duct, the junctional zone

between the glandular and squamous epithelium of the lactiferous duct and the epidermis. The rarity of Paget's disease of the nipple without an underlying intraductal carcinoma¹⁶ suggests that nipple epidermis may not be accountable as site of

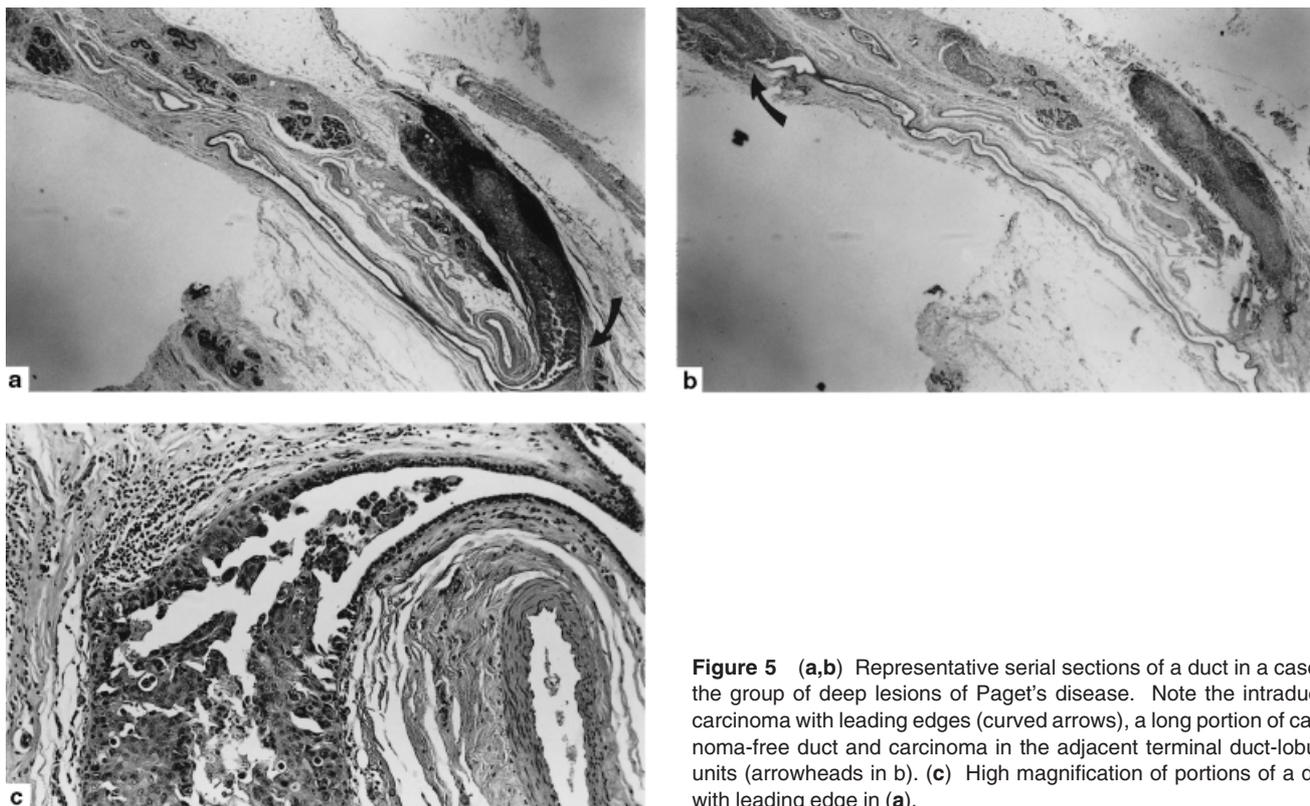


Figure 5 (a,b) Representative serial sections of a duct in a case in the group of deep lesions of Paget's disease. Note the intraductal carcinoma with leading edges (curved arrows), a long portion of carcinoma-free duct and carcinoma in the adjacent terminal duct-lobular units (arrowheads in b). (c) High magnification of portions of a duct with leading edge in (a).

origin of carcinoma for most cases in this study. It is likely that the superficial lesions in our study arose from the superficial portion of the lactiferous ducts. Support for the neoplastic potential of the superficial portion of the lactiferous duct is the occurrence of nipple adenoma associated with duct carcinoma in the same lesion.¹⁸ Evidence of the capability of the nipple epidermis to develop into Paget's disease is the occurrence of its extra-mammary counterpart and the existence of clear cells in the epidermis that have the histochemical and immunohistochemical properties similar to those of ductal cells.¹⁹⁻²¹ Expression of c-erbB-2 oncogene in most cases of mammary Paget's disease and intraductal carcinoma of comedo type and the absence of this oncogenic staining in extra-mammary Paget's disease are probably related to anatomical site of the neoplasia.

In the group of superficial lesions, in addition to tumor spread in the epidermis, there were changes suggesting that the intraductal spread downward and along the lactiferous ducts into the branching ducts in the deeper breast tissue. Supportive evidence for this direction of spread from the nipple towards the deep breast is the continuity of the intraductal carcinoma with the intraepidermal lesion and the orientation of the leading edges of the intraductal carcinoma. Therefore, it is possible that in a certain number of cases of Paget's disease associated with carcinoma in deep breast

tissue, the initial lesion could first arise from the superficial portion of the lactiferous ducts. In addition, in both groups of superficial and deep lesions, there may or may not be secondary downward spread from the epidermis with Paget's disease into other lactiferous ducts.

In this study, Paget's disease with intraductal carcinoma having skip areas was seen in at least: (i) one case of Paget's disease in the group of superficial lesions associated with a separate area of intraductal carcinoma in the deep breast tissue (these foci of intraductal carcinoma were likely located in one duct system but in separate superficial and deep areas); and (ii) one case with deeply located focus of intraductal carcinoma separated by a long portion of benign duct epithelium. Possible mechanisms of this discontinuous pattern of tumor spread are: (i) tumor cell migration; (ii) tumor implantation; and (iii) field effect.¹⁴

In conclusion, the findings in this study suggest that Paget's disease may have an origin from the intraductal carcinoma in the deep breast tissue or the superficial portion of lactiferous ducts. The lesion spreads upwards into the epidermis and downwards along the duct, with or without skip areas, into the deeper breast tissue. Although Paget's disease may appear superficial, an independent associated carcinoma in deep breast tissue with skip areas has to be ruled out.

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