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# The role of immunohistochemistry in the differential diagnosis of papillary lesions of the breast

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## ABSTRACT

Papillary lesions of the breast represent a heterogeneous group with differing biological behaviour. Correct diagnosis is crucial but may be difficult, as many benign and malignant papillary lesions have similar appearances. Immunohistochemistry plays a useful role in their differentiation. Myoepithelial markers can help in differentiating papilloma from papillary carcinoma, as the former usually shows a continuous layer of myoepithelial cells. In intracystic papillary carcinoma, there is controversy as to the presence of a complete myoepithelial cell layer around these lesions. p63 is the marker of choice as the staining is nuclear, cross-reactivity is minimal, and sensitivity is high. Papilloma may frequently be complicated by superimposed different types of epithelial hyperplasia, which range from usual to atypical or even ductal carcinoma in situ, and they may be morphologically similar. Basal cytokeratins (CKs) are useful to differentiate these entities; as usual hyperplasia is positive for basal CKs with a mosaic staining pattern. CK5/6 is probably the best marker. Neuroendocrine markers (chromogranin A and synaptophysin) may be positive in papillary carcinoma, particularly in the solid type, and there may be some overlap with the ductal carcinoma in situ with spindle cells or endocrine ductal carcinoma in situ. A panel of CK5/6, p63 and neuroendocrine markers can be useful in the diagnostic investigation of problematic papillary lesions of the breast. As the experience with these markers remains rather limited, it is too early to recommend basing treatment choices on these marker studies alone. Complete removal of lesion is probably still the treatment of choice.

Papillary lesions of the breast encompass a wide range of related entities with differing biological behaviour, and this group of lesions is characterised histologically by the presence of stromal fibrovascular cores derived from the wall of the ducts within the breast, and these ducts are frequently dilated, with protrusion of these fibrovascular cores into the ductal lumen. These fibrovascular cores are lined by epithelial cells, which may be hyperplastic or malignant. There is an intervening myoepithelial cell layer between the stromal fibrovascular cores and the epithelial cells, and this may be under-represented or absent in malignant papillary lesion. Very often many papillary lesions, being intraductal growths, are surrounded on the outside by a myoepithelial layer skirting the duct wall within which the papillary lesions arise. A somewhat similar group of lesions with intraductal epithelial proliferation with only small bulbous epithelial clusters but without genuine fibrovascular cores, termed micropapillary, is excluded from this review.

In general, benign papillary lesions can be divided into solitary and multiple papillomas, as well as florid and atypical hyperplasia within a papilloma. Malignant papillary lesions include ductal carcinoma in situ arising in a papilloma, papillary ductal carcinoma in situ, intracystic papillary carcinoma, solid papillary carcinoma as well as invasive papillary carcinoma. The histological differentiation of these lesions has been covered in the literature.<sup>1-3</sup> Correct diagnosis of this group of superficially similar but biologically distinct lesions is important because of the differences in management and outcome. Several of these papillary lesions are particularly liable to cause problem at diagnosis because of the histological similarity, and these include: (1) papilloma and papillary ductal carcinoma in situ; (2) florid epithelial hyperplasia and/or atypical duct hyperplasia in papilloma and ductal carcinoma in situ in papilloma; and (3) intracystic papillary carcinoma, solid papillary carcinoma and florid epithelial hyperplasia involving papilloma. Their histomorphological differentiation has been previously discussed,<sup>4</sup> but nevertheless the differentiation basing on morphology alone remains difficult, and can sometimes be inaccurate.<sup>5-8</sup>

In this review an immunohistochemical approach is undertaken to summarise the role of some common markers in assisting or confirming the histomorphological diagnosis of the various papillary lesions. The markers that will be discussed are divided into three categories, namely myoepithelial markers, high molecular weight basal cytokeratins (CKs) and neuroendocrine markers.

## MYOEPITHELIAL CELLS

The role of assessing myoepithelial cells in papillary lesions of the breast is twofold. The first is to identify the presence of myoepithelial cells that are interposed between the stromal fibrovascular cores and the overlying epithelial cells, and this is useful in the differentiation of papillary ductal carcinoma in situ and papilloma. The second role is to assess the presence or absence of a complete myoepithelial cell layer around the papillary lesion, particularly important in intracystic papillary carcinoma.

## PAPILLARY CARCINOMA AND PAPILOMA

There are well-cited histological criteria for this differentiation, but very often an accurate differentiation remains difficult, particularly in the setting of a needle core biopsy, which is a modality that is used increasingly in the pre-excision diagnosis of breast lesions. The frequently cited histological differences include a population of

**Table 1** The expression patterns of various papillary lesions of the breast for myoepithelial markers, basal cytokeratins, and neuroendocrine markers

Lesion	Myoepithelial markers	Basal cytokeratins	Neuroendocrine markers
Papilloma	Positive within and outside	Positive in solid areas; positive for myoepithelial cells	Negative
Papillary carcinoma, non-solid			
Papillary DCIS	Discontinuous/negative within; positive outside		Positive, low percentage
Intracystic papillary carcinoma	Discontinuous/negative within; negative outside		Positive, low percentage
Solid papillary carcinoma	Discontinuous/negative within; positive/negative outside	Negative in solid areas; variable for myoepithelial cells	Positive, high percentage

DCIS, ductal carcinoma in situ.

uniformly arranged epithelial cells with hyperchromatic nuclei and delicate arborising papillary pattern in papillary ductal carcinoma in situ, and the presence of haphazardly arranged epithelial cells with normochromatic nuclei, broader fibrovascular cores with epithelial entrapment, sclerosis and also foci of apocrine metaplasia in the typical papilloma.<sup>2-3</sup> These can be subtle, and may not be easily found in all cases. In general, it is thought that myoepithelial cells are present in papilloma and absent in papillary ductal carcinoma in situ; however, some series have demonstrated the presence of myoepithelial cells in papillary ductal carcinoma in situ in up to 46–53% of the cases.<sup>9-10</sup> Irrespective of this, in general, the myoepithelial cell layer tends to be complete in papilloma but incomplete or discontinuous in papillary ductal carcinoma in situ. Hence, immunohistochemistry is of great value in assessing the presence or absence, as well as the quantity, of the myoepithelial cells.

### INTRACYSTIC PAPILLARY CARCINOMA AND SOLID INTRADUCTAL PAPILLARY CARCINOMA

For all ductal carcinoma in situ of the non-papillary type, the malignant epithelial proliferation is located within ductal spaces, and in fact the presence or absence of a myoepithelial cell layer encircling the lesion is often used as one of the criteria for labelling the lesion to be in situ or invasive. However, in intracystic papillary carcinoma, there is recent evidence that, in contrast to previous belief, it is devoid of an overall outer myoepithelial cell layer lining, with some authors reporting that they were absent in all cases,<sup>11</sup> whereas other authors have reported absence of myoepithelial cells in about 72% of their cases.<sup>12-13</sup> This issue is not firmly settled as such.

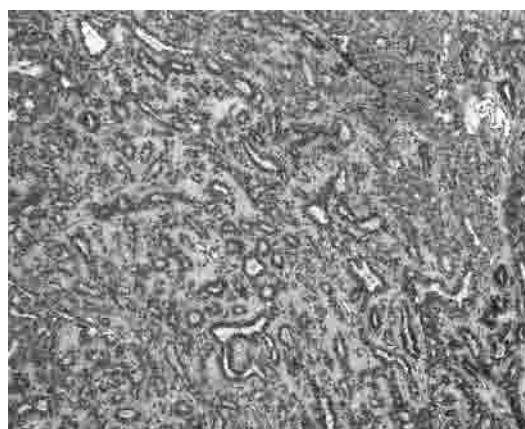
The solitary papillary carcinoma in situ is characterised by distension of ductal spaces by a large, essentially solid proliferation of malignant cells, mostly of low nuclear grade, with some showing neuroendocrine differentiation; these are termed endocrine ductal carcinoma in situ.<sup>14</sup> In contradistinction to intracystic papillary carcinoma, which is mostly solitary and nodular, solid papillary carcinoma may spread along the ductal system. For this group of lesions, some authors reported the presence of complete myoepithelial cell layer on the outside.<sup>14</sup> However there have been reported cases of solid papillary carcinoma<sup>12</sup> that showed invasion, as well as intermediate to high nuclear grade morphology, indicating that this remains a rather heterogeneous group. Significantly, they may occasionally give rise to lymph node metastases, indicating that the clinical course may not be totally indolent, and highlighting the importance of correctly identifying this group of lesions (table 1).

### MYOEPITHELIAL CELL MARKERS

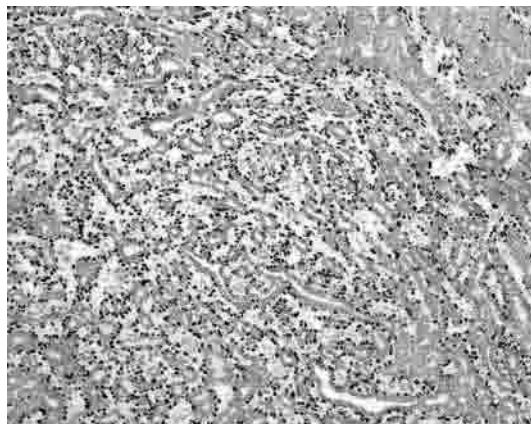
In everyday practice, there are many different myoepithelial markers to be used. The most commonly used is probably p63. In the most recently studied series of papillary lesions of the breast, p63 has been included as one of the markers for myoepithelium in virtually all series.<sup>9-17</sup> The best way to evaluate the utility of this particular marker is to evaluate the degree of positivity in benign papillomas, which theoretically should possess an almost intact layer of myoepithelial cells. The other feature requiring assessment is the degree of cross-reactivity with other non-myoepithelial cells including ductal epithelium as well as stromal fibroblasts or myofibroblasts. The overall detection rate of myoepithelial cells in benign papilloma using p63 has been reported to be high, up to 99–100%.<sup>9-10</sup> In addition there is no cross-reactivity with the epithelial cells, and the reported positive staining for stromal cells is 10%,<sup>9</sup> making this a very good myoepithelial cell marker, and probably the antibody of choice. An added advantage is that p63 staining is nuclear, unlike all other myoepithelial markers, rendering the interpretation easy and accurate (figs 1 and 2).

Calponin is another commonly used myoepithelial marker, and has been reported to be useful in the differentiation of papilloma from papillary carcinoma, particularly in the setting of needle core biopsies.<sup>17</sup> However, calponin showed cross reactivity with stromal myofibroblasts within the fibrovascular cores (fig 3).

Smooth muscle actin (SMA) is another commonly used myoepithelial cell marker. In the setting of papillary lesions of the breast, SMA can also be useful, but it faces two particular problems. (1) The sensitivity is less than p63. In a review of 100



**Figure 1** Photomicrograph of a papilloma with elaborate papillary fronds and some stromal sclerosis. Solid epithelial proliferation is not present. H&E, ×100.



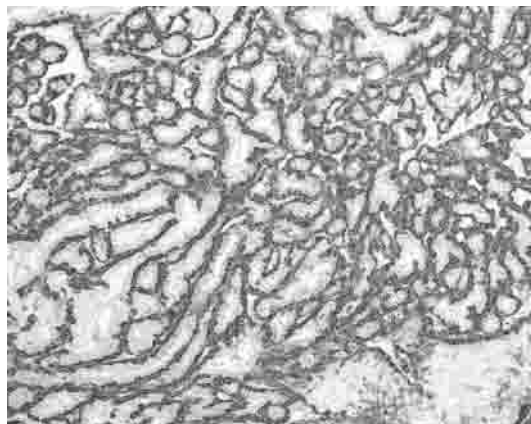
**Figure 2** Photomicrograph of the papilloma shown in fig 1. Here it shows an almost continuous myoepithelial cell layer around the fibrovascular cores by p63. The staining is nuclear.

papillomas, with 28 being involved by florid epithelial hyperplasia, SMA was able to detect myoepithelial cells in 88% (88 of 100 cases) of the lesions, compared with p63 which had a sensitivity of 99%.<sup>9</sup> (2) There was some staining of stromal cells in significant number of cases (43%), and this may create interpretative problems if the stromal myofibroblasts that were stained were located at the edge of the fibrovascular cores,<sup>9</sup> as these compressed myofibroblasts may be taken as myoepithelial cells. In another study, the staining with SMA in a series of solid papillary carcinoma was similar to that of p63, with 71% of the cases being negative for both markers<sup>12</sup> (fig 4).

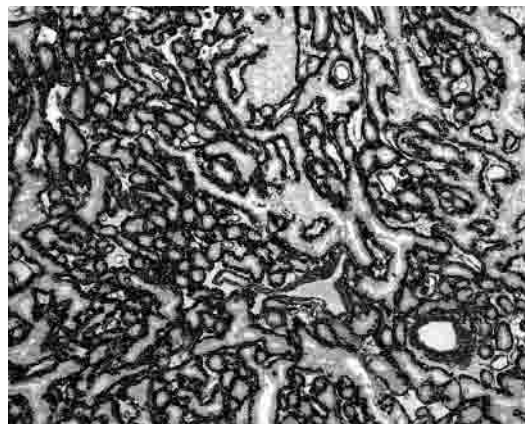
CD10, or the common acute lymphoblastic leukemic antigen, has also been demonstrated to be useful myoepithelial marker in breast lesions. In the of 100 papillomas described above, the sensitivity of CD10 was 91–93%,<sup>9</sup> and the stromal cross-reactivity was 28%, which was significantly less than that for SMA.<sup>9</sup> The presence of CD10-positive cells around the solid papillary or intracystic papillary carcinoma was detected in 0–29% of cases (fig 5, table 2).<sup>11–13</sup>

### CYTOKERATINS

CKs belong to one of the five intermediate filaments, and they function as cytoplasmic scaffolding. In general this group of intermediate filaments is considered to be the fundamental

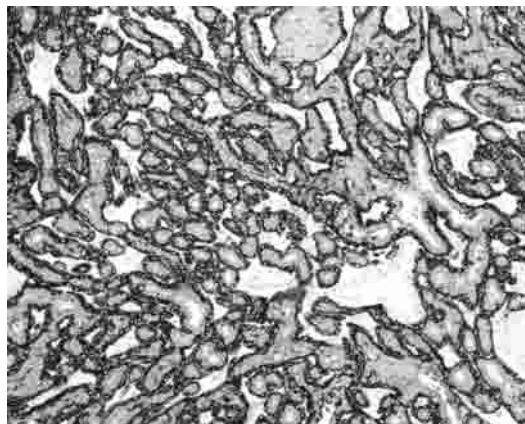


**Figure 3** Photomicrograph of the papilloma shown in fig 1. Here it shows an almost continuous myoepithelial cell layer around the fibrovascular cores stained with calponin. The staining is cytoplasmic.



**Figure 4** Photomicrograph of the papilloma shown in fig 1. Here it shows an almost continuous myoepithelial cell layer around the fibrovascular cores stained with smooth muscle actin. The staining is cytoplasmic.

expression of epithelial differentiation. The family of CKs is highly complex, and to date up to 20 CKs have been described, with CK9–20 being considered as the acidic type I and CK1–8 being considered as the neutral–basic type II.<sup>18</sup> In the normal breast, the ductal epithelial cells express simple epithelial CKs (CK7, 8, 18 and 19); conversely the basal-type CKs (CK5, 6 and 14) are expressed in the myoepithelial cells.<sup>19–20</sup> Many previous studies have evaluated the differential expression of different CKs in various types of epithelial proliferation, ranging from benign to malignant. Basal-type CKs are expressed in the usual epithelial hyperplasia, ranging from 88 to 100%<sup>21–23</sup> whereas the expression in atypical to malignant epithelial proliferations is reported to be much more infrequent, ranging from 4% to 23%.<sup>21–23–24</sup> Similar results have also been obtained for infiltrating duct carcinomas.<sup>25–26</sup> There is molecular evidence to account for this difference. By using western blot technique, it has been demonstrated that usual and florid epithelial hyperplasia is derived from progenitor or adult stem cells that give rise to glandular or myoepithelial cells, whereas atypical epithelial hyperplasia or ductal carcinoma in situ display the differentiated glandular CK phenotype.<sup>24</sup> This has been further substantiated by a comparative genomic hybridisation study for gross genetic changes, in which 42 benign breast lesions (including usual epithelial hyperplasia, papilloma, tubular



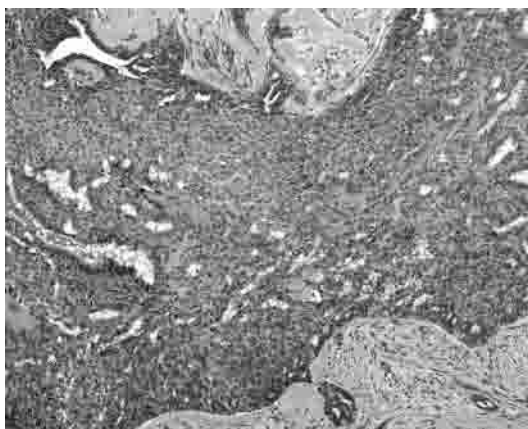
**Figure 5** Photomicrograph of the papilloma shown in fig 1. Here it shows an almost continuous myoepithelial cell layer around the fibrovascular cores stained with CD10. The staining is cytoplasmic.

**Table 2** The sensitivity, specificity, and positive and negative predictive values of various myoepithelial markers to differentiate papilloma (positive for myoepithelial cells) from papillary carcinoma (including intracyclic papillary carcinoma) (negative for myoepithelial cells)

Marker	p63 (%)	Calponin (%)	SMA (%)	CD10 (%)
Location of myoepithelial cells: inside the lesion				
Sensitivity	82–99	93	88	78–91
Specificity	57–87	79	65	72–75
Positive predictive value	77–79	74	83	57–83
Negative predictive value	89–97	94	78	84–85
Location of myoepithelial cells: around the lesion				
Sensitivity	73–100	100	–	100
Specificity	100	100	–	100
Positive predictive value	100	100	–	100
Negative predictive value	100	100	–	100

SMA, smooth muscle actin.

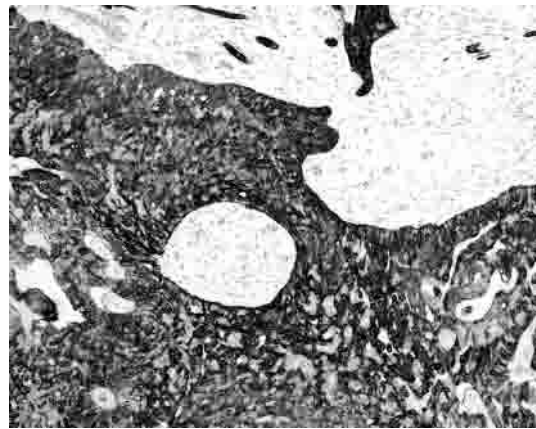
adenoma and adenosis) did not show any detectable genomic changes, whereas the 42 cases of ductal carcinoma in situ of differing grades demonstrated significant genomic aberrations with low HMW CK expression.<sup>22</sup> While the differentiation of usual and atypical epithelial hyperplasia based on expression of basal CKs seems to be quite accurate, a word of caution is in order. This high accuracy cannot be extrapolated to differentiate between benign and malignant breast lesions in general. In a detailed study involving more than 400 breast lesions, it has been reported that moderate to strong expression of basal CKs can help to differentiate usual epithelial hyperplasia (97% moderate to strong staining) and atypical duct hyperplasia and ductal carcinoma in situ (4–7% moderate to strong staining), the expression patterns of other lesions were less clear cut. The expression rate was much lower than usual epithelial hyperplasia, for papilloma and other benign lesions it was only 34–50%. In addition, atypical hyperplasia or lobular carcinoma in situ may also show significant staining of basal CKs in 17–25% of cases.<sup>23</sup> Thus the use of basal CKs is most reliable when one is dealing with the “solid” areas of epithelial proliferation within a papilloma, to determine whether the proliferation is benign usual hyperplasia or atypical to malignant epithelial hyperplasia. The utility of this group of markers in dealing with the “papillary” area of a papillary lesion is less dependable. The staining pattern of these basal CKs in usual epithelial hyperplasia is characteristically mosaic or heterogeneous in pattern (table 1).<sup>10 19 27</sup>

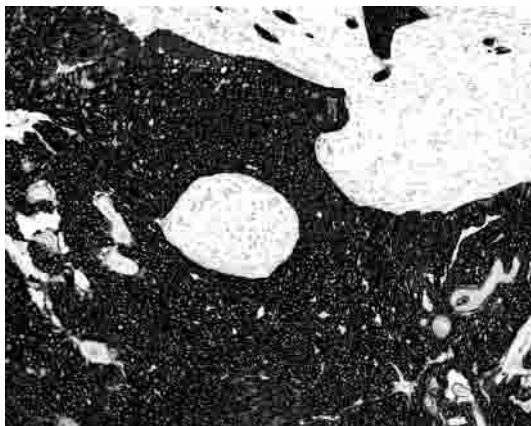
**Figure 6** Photomicrograph of a papilloma involved by solid epithelial proliferation of the usual florid hyperplastic type. There is widened spacing of the fibrovascular cores, and the epithelial cells show nuclear streaming. H&E, ×100.**BASAL CK MARKERS**

In everyday practice, the basal CKs are usually in the form of cocktails. Of these, either CK5/6 (CK5/6) or 34βE12 (recognises CK1, 5, 10 and 14) are the most commonly used.

In the setting of papillary lesions, CK5/6 has been shown to be useful. The staining of CK5/6 is cytoplasmic and membranous, and it has been reported to be positive in 84–100% of usual ductal hyperplasia within papillomas,<sup>16 28 29</sup> in contrast to the atypical hyperplasia or carcinoma in situ within papillomas, in which the staining was either negative or weak, and in only up to 2%<sup>16 28 29</sup> of the cases. In needle core biopsies, this marker has been shown to be of value in helping to improve the diagnostic accuracy to correctly classify the papillary lesions.<sup>15 17</sup> In addition, CK5/6 has the advantage of being easy to interpret. The strong staining in the epithelial cells of the usual hyperplasia, the mosaic pattern,<sup>10</sup> and the high percentage of epithelial cell staining (50–80%)<sup>16 28</sup> facilitate interpretation. One potential fallacy is in cases of atypical ductal hyperplasia or ductal carcinoma in situ involving papillomas: there may be occasional staining of the entrapped benign epithelial or myoepithelial cells. But the small number of such stained cells, the close proximity to the stromal fibrovascular cores, and the absence of the mosaic pattern, will help to differentiate this false positivity from the true positivity in the usual epithelial hyperplasia (figs 6 and 7).

Another commonly used basal CK cocktail is 34βE12, which detects CK1, 5, 10 and 14. In the differentiation of different

**Figure 7** Photomicrograph of the papilloma shown in fig 6. Here it shows involvement by solid epithelial proliferation of the usual florid hyperplastic type, stained with cytokeratin 5/6. There is strong positivity of the epithelial cells.

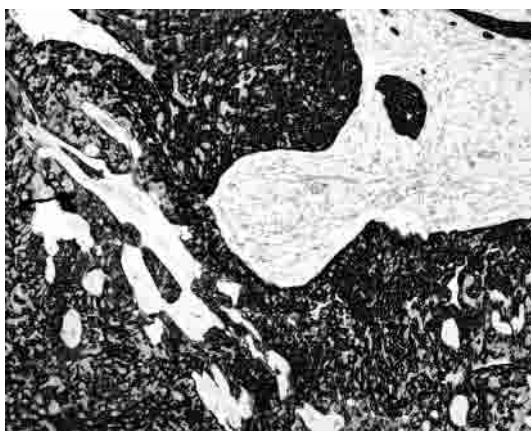


**Figure 8** Photomicrograph of the papilloma shown in fig 6. Here it is shows involvement by solid epithelial proliferation of the usual florid hyperplastic type, stained with 34βE12. There is strong positivity of the epithelial cells.

types of epithelial hyperplasia, the staining pattern and characteristics are similar to CK5/6. Moderate to strong staining intensity of 34βE12 occurred in 76–100% of usual epithelial hyperplasia.<sup>10 16 29</sup> In atypical epithelial hyperplasia or ductal carcinoma in situ, the staining was 0–20% of the cases (fig 8).<sup>10 16 19</sup>

CK14 is another antibody that is less commonly used for this purpose of differentiation. It was reported to be positive in more than 95% of usual epithelial hyperplasia within papillomas<sup>9 16</sup> but also in 12–20% of ductal carcinoma in situ involving papillomas (fig 9).

While CK5/6 and 34βE12 are both commonly used cocktails of basal type CKs, is one of these better than the other? In most series in the literature dealing with basal CKs, one of these was used.<sup>10 13 15 23 28</sup> Only in a handful of studies have both antibodies been compared,<sup>16 29</sup> and these have demonstrated that, compared with 34βE12, CK5/6 has a higher sensitivity, specificity, positive predictive value and negative predictive value in identifying the usual type of ductal epithelial hyperplasia,<sup>16 29</sup> and indeed the sensitivity and negative predictive value has been reported to be 100% in one of the series.<sup>16</sup> CK14 also showed a high specificity and positive predictive value, comparable with that of CK5/6, and it is also better than 34βE12.<sup>16</sup>



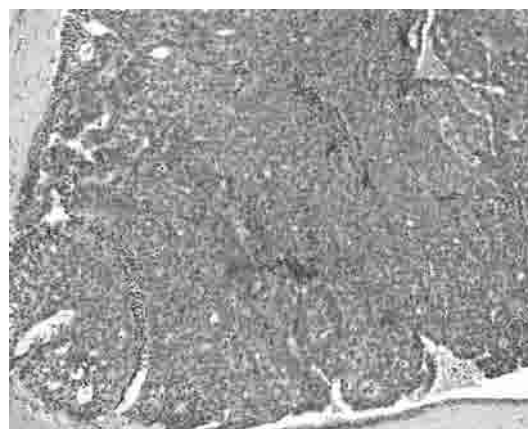
**Figure 9** Photomicrograph of the papilloma shown in fig 6. Here it is shows involvement by solid epithelial proliferation of the usual florid hyperplastic type, stained with cytokeratin 14. There is strong positivity of the epithelial cells.

**Table 3** Sensitivity, specificity, positive and negative predictive values of various basal CKs to differentiate papilloma (positive for basal CKs) from papillary carcinoma (negative for basal CKs)

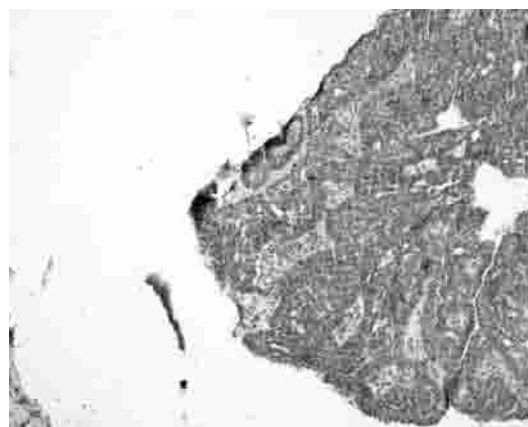
Parameter	CK5/6 (%)	34βE12 (%)	CK14 (%)
Sensitivity	84	76	92–100
Specificity	100	80	78–100
Positive predictive value	100	79	66–100
Negative predictive value	86	77	95–100

Location of staining: solid areas of epithelial proliferation within papillary lesions. CK, cytokeratin.

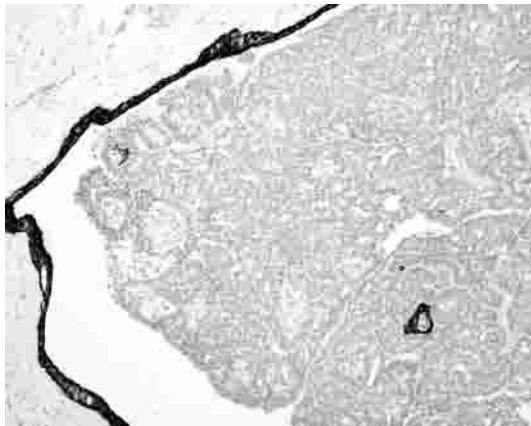
Of note is that basal CKs are also expressed by myoepithelial cells and in almost all cases, the myoepithelial cell layer is also highlighted by any stains within this group. CK5/6 has been reported to be positive in the myoepithelial cells in “nearly all” normal breast tissue and benign and malignant breast lesions in a series of almost 700 cases,<sup>23</sup> and the sensitivity of CK14 in detection of myoepithelial cells in papillomas was 95%,<sup>9</sup> (table 3).



**Figure 10** Photomicrograph of a solid papillary carcinoma present within a distended ductal space. The fibrovascular cores are broad and infrequent, with intervening epithelial proliferation in a solid pattern. H&E, ×100.



**Figure 11** Photomicrograph of the solid papillary carcinoma shown in fig 10. Here it is present within a distended ductal space, stained with synaptophysin. The epithelial cells show granular cytoplasmic staining.



**Figure 12** Photomicrograph of the same solid papillary carcinoma shown in fig 10. Here it is present within a distended ductal space, stained with cytokeratin 5/6. The epithelial cells show negative staining.

### NEUROENDOCRINE MARKERS

The commonly used neuroendocrine markers include chromogranin A and synaptophysin. The usefulness of these markers in the diagnosis of papillary lesions has not been extensively studied. In a very interesting study, it was found that neuroendocrine markers were consistently negative in benign papilloma, whereas, in papillary carcinoma, the positivity rate was 35% (16 of 45 cases) (figs 10 and 11). When this latter group was further subdivided into solid and non-solid types, the positivity rate of these neuroendocrine markers became 67% (14 of 21 cases) for the solid type, and 8% (two of 24 cases) for the non-solid type.<sup>13</sup> This observation is likely to reflect partial overlap with the disease entities like endocrine ductal carcinoma in situ,<sup>14</sup> ductal carcinoma in situ with spindle cells (spindle cell

**Table 4** Sensitivity and specificity, and positive and negative predictive values, of neuroendocrine markers to differentiate papilloma (negative for neuroendocrine markers) from papillary carcinoma (positive for neuroendocrine markers)

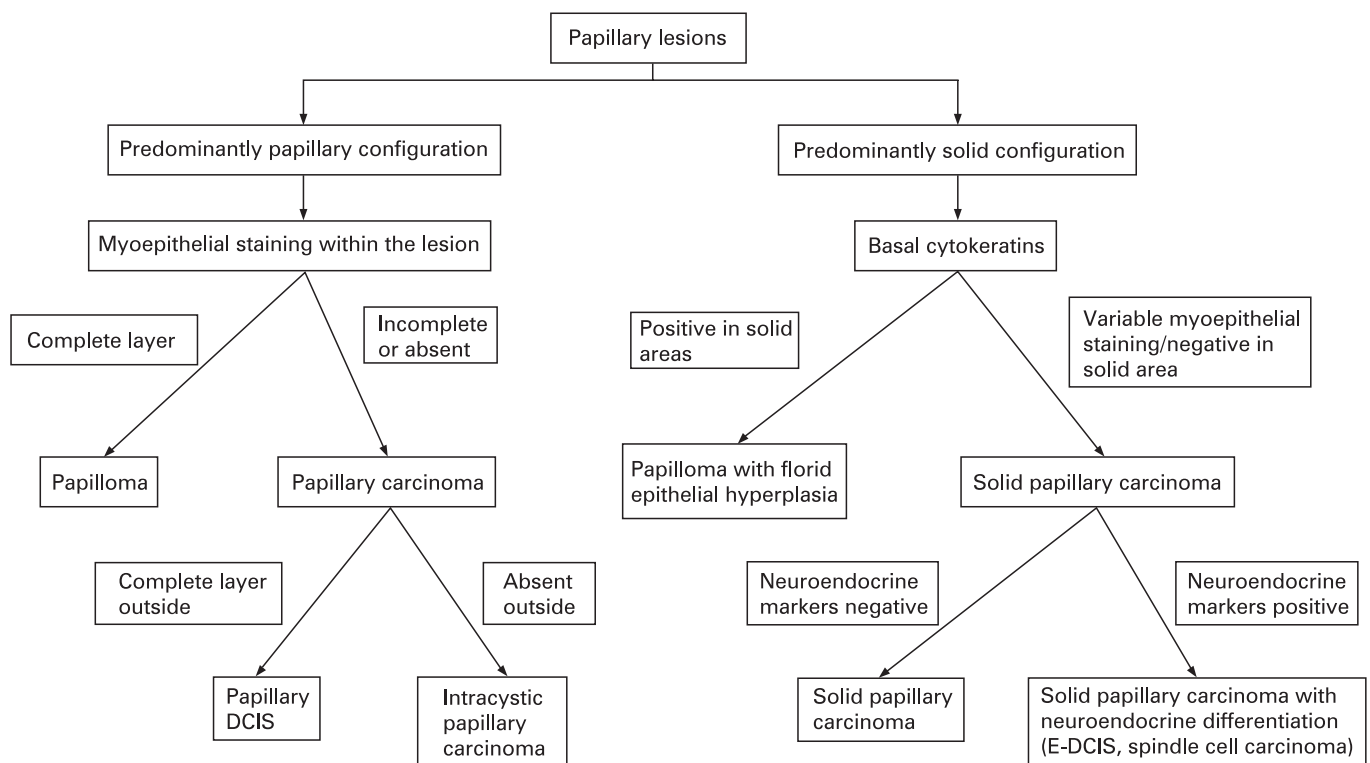
Parameter	Neuroendocrine markers (%)
Sensitivity	35–50
Specificity	100
Positive predictive value	100
Negative predictive value	38

Location of staining: epithelial cells.

carcinoma),<sup>30 31</sup> or solid papillary carcinoma with neuroendocrine-like component.<sup>32 33</sup> In the spindle cell ductal carcinoma in situ, neuroendocrine markers are expressed in 72% of the tumour cells,<sup>30</sup> and in the solid papillary carcinoma, a significant proportion (30–50%) also express neuroendocrine markers.<sup>32 33</sup> Basing on histology, the diagnosis of spindle cell carcinoma in situ is particularly problematic. As the spindle cells are usually bland and may also show organoid arrangement, resembling streaming, they can be mistaken for florid epithelial hyperplasia involving a papilloma.<sup>14 30 31</sup> When such a differential diagnosis is being considered, staining with basal CKs and neuroendocrine markers is extremely helpful. In papillomas with florid epithelial hyperplasia, they are negative for neuroendocrine markers (specificity 100%),<sup>13 30</sup> and in spindle cell carcinoma, they are also negative for basal CKs (specificity 100%) (fig 12),<sup>13 30 31</sup> although the expression rate of neuroendocrine markers is more variable (50–72%) (tables 1 and 4).<sup>13 30</sup>

### CONCLUSION

Differentiation of papillary lesions can be difficult, and immunohistochemistry using common markers can be very



**Figure 13** Paradigm of approach to papillary lesions using a panel of immunohistochemical stains. DCIS, ductal carcinoma in situ.

## Take-home messages

- ▶ Diagnosis of papillary lesions of the breast is difficult, and requires clinical, histological and immunological evaluation.
- ▶ Cytokeratin 5/6, p63 and neuroendocrine markers can be used as an initial panel for investigation of papillary lesions.
- ▶ Experience of diagnosing papillary lesions basing on immunohistochemistry alone is limited, and excision should still be considered the standard of care.

helpful. Myoepithelial cells tend to be present in a complete layer lining the stromal fibrovascular cores in papilloma, whereas it may be absent or may form an incomplete layer in papillary carcinoma. Intracystic papillary carcinoma may possess an intact, incomplete or absent myoepithelial layer in the periphery. Of all the commonly used markers, p63 shows the best results with highest sensitivity and lowest cross reactivity, and the nuclear staining is easy to interpret. Basal CKs are useful to differentiate between the different types of epithelial hyperplasia (usual, atypical or ductal carcinoma in situ), with usual hyperplasia being usually positive and the atypical to malignant proliferations being negative. The staining is strong and is present in the majority of the cells, facilitating interpretation even in small samples, as in core biopsy. CK5/6 appears to have a better sensitivity and specificity than other markers. This marker will also highlight myoepithelial cells. Neuroendocrine markers are useful in differentiating solid papillary carcinoma (spindle cell type, neuroendocrine type) from papilloma with extensive florid epithelial hyperplasia. When coupled with basal CKs, a very high specificity can be achieved. This is summarised in the paradigm (fig 13).

While CK5/6, p63 and neuroendocrine markers can be used as an initial panel of investigation when one is dealing with problematic papillary lesions of the breast, the results (and hence the subsequent management plans) need to be interpreted with great caution as the number of cases studied using these markers is not high, and for the individual marker, the sensitivity and specificity are not absolute. At the current stage, immunostaining with these markers serves as a useful adjunctive diagnostic tool, but complete removal of all papillary lesions with full histological assessment should remain as the standard of care practice in the management of this group of problematic breast lesions.

**Competing interests:** None.

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