Intracystic Papillary Carcinoma of the Breast: 
A Diagnostic Challenge with Major Clinical Impact

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Abstract. Background: Intracystic papillary carcinoma (IPC) is a ductal carcinoma of papillary variety that develops in a cystic space surrounded by a fibrous capsule. It is a rare clinicopathological entity, the in situ or invasive character of which is difficult to establish, particularly on biopsy. The treatment is surgical and breast conservation depends on the tumor size. Lymph node exploration is still debated. The diagnosis of IPC is a challenge for the pathologist: the negativity of the basement membrane markers and of myoepithelial cells carries a risk of over-diagnosis on biopsy that can lead to over-treatment. Case report: To illustrate this risk, we report the case of a breast mass of 8 cm; its biopsy evoked invasive papillary carcinoma (no hormone receptors and overexpression of Human Epidermal Receptor-2 (HER-2) and for which neoadjuvant chemotherapy associated with trastuzumab was firstly proposed. Results: The analysis of all anatomical radio-clinical data in a multidisciplinary context, however, allowed suspecting IPC, thus leading to first-line surgery (mastectomy with negative sentinel lymph nodes). With this diagnosis being confirmed on surgical specimen, no systemic treatment was then necessary. After 48 months, the patient is in complete remission.

Intracystic papillary carcinoma (IPC) is a rare disease, accounting for 0.5 to 2% of all breast neoplasms. Some cases have been described in males (1-3). IPC occurs most often in the form of a single mass preferentially after menopause (4). IPC was described for the first time in 1969, by McKittrick (5), as a variant of papillary ductal carcinoma developed in a cyst and surrounded by a fibrous capsule. Because it is well-circumscribed and with indolent clinical behaviour, it has traditionally been considered as a variant of ductal carcinoma in situ (DCIS) (6). Recently, its affiliation with DCIS was questioned because of the depleted layer of myoepithelial cells up to its complete absence, thus considering IPC as an invasive ductal carcinoma of low aggressiveness (7, 8). However, the positivity of the basement membrane type IV collagen led other authors to consider IPC as DCIS (9). The presence of a residual layer of myoepithelial cells, as reported by several teams (9, 10), strengthened the hypothesis that IPC would grow at the expense of an underlying intracystic papilloma. The expansive growth of cancerous proliferation would entrap remaining myoepithelial cells until their disappearance. Recently, Khoury et al. (11), using a technique of comparative genomic hybridization, showed that the molecular changes observed in IPCs were more similar to DCIS than invasive ductal carcinomas, thus explaining their favourable prognosis.

Despite the abundant literature on IPC, few publications deal with its therapeutic management, including the terms of surgery (place of sentinel lymph node biopsy or axillary dissection) and the benefits of radiotherapy and hormone therapy. The aim of our observation was to make an update on the therapeutics to be considered, avoiding over-treatment.

Case Report

A 58 year-old post-menopausal patient, was seen in March 2010 for a second medical opinion. Clinical examination revealed, at the upper-middle and retro-areolar area of the left breast, a rounded and flexible mass, 8×10 cm in diameter. Examination of the axilla did not find pathological lymph nodes. Mammography allowed to view a rounded opacity of 10 cm of diameter associated with several parenchymal opacities partially calcified evoking former fibroadenomas (Figure 1 A1, A2). Ultrasound highlighted a cystic lesion measuring 9×7 cm in diameter, with wall thickening and, at its inferolateral edge, two tissue vegetations measuring 3×2.2 cm and 1.3×0.5 cm, respectively (Figure 1B). The nuclear magnetic resonance

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examination confirmed the data and the absence of other homo- or contralateral lesions (Figure 1C). The initial microbiopsy performed by the first radiologist found a papillary carcinoma described as infiltrating grade I (according to Elston and Ellis), with no expression of hormone receptors (estrogen receptor ER/ progesterone receptor PR-negative) and overexpression of human epidermal receptor HER-2 (score 3+). The initial staging including a dosage of cancer antigen CA 15-3, chest radiography and abdominopelvic ultrasound was normal. Given the tumor size, the "invasive" nature of the proliferation, the absence of hormone receptors and the HER-2 overexpression, neoadjuvant chemotherapy combined with trastuzumab was proposed to the patient and a central venous access device was inserted (Figure 1A1, A2).

However, a second opinion was required to the regional referral centre for breast disease before starting chemotherapy. Given the cystic nature of the tumor, the presence of a perilesional capsule and the papillary appearance of cells on the biopsy, the diagnosis of IPC was discussed and a first-line surgery was decided. Because of tumor size, mastectomy was proposed to the patient associated with a sentinel lymph node biopsy with intraoperative examination of sentinel lymph nodes. Immediate breast reconstruction was proposed, but the patient did not accept it.

At macroscopic examination, the mastectomy specimen measured 25×20×5 cm and its section showed a 10×9×5 cm cyst which included in its wall a 2.5 cm major axis tumor corresponding to a well-limited papillary proliferation developed in a cyst with no displayed infiltration (Figure 2A). There was marked cytonuclear atypia with numerous mitoses (20 mitoses in 10 fields at a magnification of 400, or 8.4 mitoses/mm²). Papillary proliferation showed apocrine aspects and necrosis territories (Figure 2B). The rest of the breast tissue showed clusters of atypical lobular hyperplasia and two intra-mammary lymph nodes with no malignancy. There were also four fibroadenomas with diameters between 0.8 and 1.5 cm, one of them being colonized by atypical lobular hyperplasia. The 5 sentinel lymph nodes, negative on

Figure 1. Imaging of breast intracystic papillary carcinoma. A1. Oblique-view mammography. A2. Front-view mammography. For A1 and A2, we can see on the right side (R), fibroadenomas and a central venous access device, and on the left (L) a cystic mass of 10 cm in diameter, associated with several partially calcified masses. B. Ultrasound of the left cystic mass, measuring 9×7 cm; it has a thickened wall with two tissue vegetations at its inferolateral edge. The first vegetation measures 3×2.2 cm and the second 1.3×0.5 cm. C. Nuclear magnetic resonance imaging of the left breast. The cystic lesion shows a thickened wall with tissue vegetation.
frozen section, were analyzed for final examination after staining with an anti-pan-keratin antibody (clone AE1-AE3, Dako®, Les Ulis, France) in multiple serial section levels (500 microns). This second analysis confirmed that they were free of metastasis. Immunohistochemistry with anti-smooth muscle (anti-actin, clone 1A4, Dako® Les Ulis, France), anti-p63 (clone 4A4, Ventana®, Bâle, Suisse), and anti-collagen IV (clone CIV22, Dako®, Les Ulis, France), showed a myoepithelial cell layer at the level of the cyst lining and in some fibrovascular axes (Figure 2C).

Such histology confirmed the diagnosis of IPC. The central venous access device was removed and chemotherapy was not performed. Because of negative hormone receptors, no hormonal therapy was prescribed. After four years of follow-up, the patient is in complete remission.

Discussion

Diagnosis as well as morphological classification and prognosis of papillary lesions have often been a challenge for pathologists (10). Immunohistological studies help differentiate on the one hand benign from malignant lesions and, on the other hand, among malignant lesions, localized (in situ) lesions from invasive lesions. There is no completely discriminant marker for such discrimination but it is the combination of different markers that optimizes results. The first description of IPC was published in 1969 (5). In 1983, Carter (12) considered IPC as a form of DCIS because of its nodular growth without associated desmoplastic reaction and its non-aggressive behaviour. Nevertheless, the impossibility to highlight the myoepithelial cell layer by immunohistochemistry did put into question the in situ nature of IPC (13). The complete absence of basement membrane and myoepithelial layer in a series of 22 IPCs tested for five immunohistochemical markers led Collins (8) to conclude that IPC represented a form of encapsulated invasive carcinoma, i.e. surrounded by a fibrous reaction leading to the formation of a capsule. In our case, the diagnosis of invasive ductal carcinoma proposed on biopsy was not retained, considering the papillary architecture, the very limited nature of the tumor, the absence of desmoplastic stroma reaction and finally the positivity for anti-p63 (clone 4A4, Ventana®, Bâle, Suisse) of the myoepithelial cell layer lining the cyst. In IPC, the lesions may have a heterogeneous appearance with a ductal component that can be found

Figure 2. Histological and immunohistochemical aspects of breast intracystic papillary carcinoma. A. The IPC grows in a thickened fibrous wall cyst (×20). B. Nuclear pleomorphism is moderate to marked with necrosis areas (×200). C. Collagen IV stresses persistence of the basement membrane at the cyst wall and in some rare papillary structures (×100).
embedded in the fibrous tissue, thus giving a false image of invasion. In our case, the puncture route was found in the analysis of the surgical specimen and corresponded indeed to an area where small channels seemed to infiltrate a fibrous stroma. In this territory, the anti-p63 antibody marked rare myoepithelial cells stretched in fibrosis.

The prognosis of IPC is excellent (13, 14), but local recurrences have been observed (10). After conservative treatment, the role of local radiotherapy is not consensual; however, after complete mastectomy, radiotherapy is not retained, as for our patient (10). A low nodal involvement rate was observed in large IPCs (14, 15). Therefore, in the absence of contraindication, sentinel lymph node biopsy seems to be useful for supracentimetric IPCs (10) and avoids the morbidity associated with complete axillary dissection. Contrary to what we observed in our patient, the IPCs are most often hormone-sensitive and in this case adjuvant hormonal therapy is recommended (10). Regarding the overexpression of HER-2 in a case of IPC, to our knowledge, no other observation was published. Its meaning is, therefore, not established. Therapeutically, in the same manner as what is observed in positive DCIS for HER-2 (16), no treatment with trastuzumab is indicated.

Our case is a good illustration of the risks of overtreatment induced by lack of knowledge of IPC. In the absence of a second opinion from a specialised unit in the management of breast diseases, the patient would have received inadequate treatment with chemotherapy and trastuzumab followed by a mastectomy with complete axillary dissection, radiotherapy and continued treatment with trastuzumab, with morbidity and high costs associated with all these approaches.

To conclude, IPC is a rare form of breast carcinoma, the in situ or invasive character of which is difficult to determine for the pathologist. Lack of knowledge of this clinicopathological entity may lead to over-diagnosis and then over-treatment. Direct confrontation of the pathologist, radiologist, surgeon and oncologist is particularly useful in the presence of this rare, difficult to diagnose, disease.

References


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