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Clinical and radiological presentation of pleomorphic lobular carcinoma in-situ and its association with invasive malignancy

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ABSTRACT

Aims: Optimal management of Pleomorphic lobular carcinoma-in-situ (PLCIS) remains a matter of debate. We aimed to identify presenting clinical, radiological and histopathological features and oncological outcome of PLCIS.

Methods: From a prospectively maintained histopathology database between January 2000 and June 2014, all patients with a diagnosis of PLCIS were identified, and retrospective review of case notes performed.

Results: Of 19 cases, only 3 presented as symptomatic lumps, however 11 had mass lesions on imaging. All patients underwent definitive cancer surgery with wide margins. In all but three cases, PLCIS was associated with additional pathologies (DCIS, ILC, IDC), highlighting the pluripotential development of breast cancer. Of the six cases with no invasion, three were oestrogen receptor negative. There were no local or systemic recurrences over the median follow up period of 66 months.

Conclusion: PLCIS presenting without invasion is rare and, unlike invasive cancer and ductal carcinoma-in-situ, does not appear to be predominantly associated with ER positivity. However, PLCIS is almost universally associated with invasive cancer or DCIS, and should be managed with wide excision and clear margins.

Clinical practise points:

- There is uncertainty surrounding the management of PLCIS as highlighted by the lack of guidelines on this unusual disease entity.
- The commonest presentation of PLCIS is in asymptomatic women through breast screening.
- PLCIS presenting without invasion is rare and unlike invasive breast cancer and DCIS, does not appear to be predominantly commonly associated with ER positivity.
- PLCIS is commonly associated with in-situ and invasive lesions, with 58% of cases associated with invasive lobular carcinoma in this current series.
- Breast conserving surgery with clear margins and adjuvant treatment as dictated by associated pathology and molecular profile is recommended for PLCIS.
- In patients presenting with a mass lesion, and pure PLCIS on diagnostic core biopsy: A re-biopsy, ideally using vacuum-assistance is recommended, to attempt to upgrade the tumour pre-operatively, as invasion is almost universal in this subset.The common association of PLCIS with the presence of invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in-situ and lobular carcinoma-in-situ suggests a single pluripotent stem cell origin for these cancer subtypes.

1. Introduction

Pleomorphic Lobular Carcinoma-in-situ (PLCIS) is a rare and distinct variant of lobular carcinoma-in-situ (LCIS), with many pathological features in common with high grade ductal carcinoma-in-situ (DCIS). PLCIS was described only as recently as 1996 [1]. The defining histological and radiological features are distended

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lobules with enlarged and dyscohesive cells with eccentric nuclei and abundant eosinophilic cytoplasm. PLCIS is regularly associated with comedo necrosis with associated calcification and hence is often detected on mammogram as opposed to classical LCIS. Historically, it has been difficult to differentiate PLCIS from DCIS due to similar histological features but immunohistochemistry staining has helped to differentiate these two entities. Immunohistochemistry staining for E-cadherin can differentiate lobular from ductal carcinoma in-situ because membranous staining is observed in most DCIS, unlike LCIS. Similarly, PLCIS stains negatively for E-cadherin, despite morphological similarities with DCIS.

The histological differentiation of classic LCIS from PLCIS is clinically important as the limited published literature suggests that the two entities have very different clinical behaviour, risk and therefore different surgical management. The optimal clinical treatment for patients with PLCIS is unknown, but current consensus is that these lesions closely resemble high grade DCIS pathologically and should be treated in a similar manner.

The aims of this study were to determine the clinical and radiological presentation of PLCIS. In order to clarify appropriate oncological management of this entity we aimed to understand the association of this lesion with other breast pathologies and explore the risk of recurrence with current treatment regimens.

2. Material and methods

In a single tertiary referral NHS Breast Screening Unit, treating approximately 700 new breast cancers per annum, all (consecutive) patients diagnosed with PLCIS between January 2000 and June 2014 were identified from the prospectively maintained breast histopathology database. Manual retrospective review of case notes was performed for all PLCIS patients identified in the database.

In our unit, all mammograms are read by two consultant breast radiologists and all suspicious lesions are discussed in a multidisciplinary forum to establish the need for further investigation and treatment. All suspicious lesions undergo radiological guided tru-cut core biopsy, with proven PLCIS, DCIS and invasive cancers being treated with either breast conserving wide local excision or mastectomy. All histopathology is reported by two pathologists according to National Health Service Breast Screening Programme (NHSBSP) guidelines. Management is discussed at a multidisciplinary meeting and patients followed up with annual clinical examination and mammography for a minimum of 5 years.

2.1. Pathological data and immunohistochemistry

The types of tumour, size, grade and margin status were assessed according to NHSBSP Quality Assurance standards and prospectively recorded on all patients. Methods for ER, PR, HER2 and Ki67 have been previously described [2]. Immunostaining was nuclear for Ki67, ER and PR and predominantly cell membranous for HER2 with a cytoplasmic component. For each section, a minimum of 1000 cells were scored across randomly selected areas of tumour at a magnification of $\times 400$ using a grid graticule cell counter. Ki67, ER and PR scores were calculated as a percentage of positively stained nuclei (i.e. positive cells/total number of cells $\times$ 100%). Steroid receptor staining intensity was reported using the quick (Allred) score as per NHS BSP Pathology Reporting Guidelines [3], a score of three or above taken to be ER positive. E-cadherin immunohistochemistry staining is performed on a Roche BenchMark Ultra machine using Roche anti E. cadherin antibody. Roche DAB detection kit was used as the visualisation technique as per standard Roche methodology.

3. Clinical management

All patients had definitive cancer surgery which was either wide local excision or mastectomy. Clear margins were determined as ≥ 1 mm. Adjuvant radiotherapy was administered to all patients with invasive disease, and to patients with in-situ disease and breast conserving surgery on a case-by-case basis following discussion at a multidisciplinary team (MDT) meeting. Adjuvant chemotherapy was recommended on a case-by-case basis to patients with invasive disease as per MDT discussions. All ER positive patients were treated with adjuvant endocrine therapy.

4. Results

Nineteen patients were diagnosed with PLCIS over the 13 year study period. Age at diagnosis was a median of 62 years (range 48–79). The follow-up period was a median of 66 months (range 1–127).

4.1. Presentation, radiology and pathology

Fifteen patients were asymptomatic and diagnosed through the NHSBSP and three patients presented to clinic with a lump. One additional patient (patient 4) was found to have PLCIS as an incidental finding of microcalcifications on mammogram in a symptomatic clinic.

The three symptomatic cases had palpable masses which were visible on mammograms and ultrasound. Two of these masses were confirmed as invasive lobular carcinoma on core biopsy and at surgical excision PLCIS was found associated with the tumours (Table 1). The other symptomatic patient (patient 2) presented with a large mass clinically and was found to have 70 mm of micro calcification and distortion on mammography and a 50 mm mass on ultrasound. Diagnostic core biopsy and surgical excision specimens confirmed PLCIS alone.

The screen-detected patients consisted of: seven patients with micro calcifications alone, six patients with a mass visible on mammography and two patients with both micro calcifications and a mass.

Of the 11 patients with a pre-operative diagnosis of PLCIS, two were preoperatively found to have invasive cancer, a further four were found to have cancer at definitive surgery and a further two patients had associated DCIS.

Of all 19 patients with PLCIS, only three patients had PLCIS in isolation, with no additional invasion or DCIS.

In total, six of 19 patients had in-situ disease only, of which only patient 5, and possibly patient 12, had strongly oestrogen receptor [ER] and progesterone receptor [PR] positivity, with 3 patients having ER-negative disease highlighting the more aggressive phenotype of PLCIS.

4.2. Management

All 19 patients had definitive cancer surgery which was wide local excision in fifteen and mastectomy in four. Clear margins were determined as ≥ 1 mm. One patient required re-excision to clear the margins. The median tumour size was 20 mm (range 5–50 mm). Thirteen patients received adjuvant radiotherapy, of which one had received radiotherapy for large tumour size following mastectomy. Only one patient with 22 mm, grade 3, ER/PR positive invasive lobular cancer received adjuvant chemotherapy. All ER positive patients were treated with adjuvant endocrine therapy. There were no local or systemic recurrences over the follow-up period (median of 66 months).