Section: Pathology

Original Research Article

REGRESSIVE CHANGES OF DUCTAL CARCINOMA IN SITU IN ASSOCIATION WITH EXTENT OF DISEASE, INFLAMMATION AND HORMONE RECEPTOR PROFILE

Akshita Agarwal[1], Deepika Hemrajani[2], Prerana Choudhary[3], Subhash Chandra Sharma[4]

[1]Senior Medical Officer, RUHS, Jaipur, Rajasthan, India.
[2]Professor, [3]Assistant Professor, [4]Associate Professor, Department of Pathology, Sawai Man Singh Medical College, Jaipur, Rajasthan, India.

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Corresponding Author:
Dr. Subhash Chandra Sharma,
Email: drsubhash444@gmail.com

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Abstract

Background: Tumor regression is continuum of changes leading to fibrosis, obliteration and effacement of neoplastic population in wide spectrum of malignancies like melanoma, prostrate etc. Ductal carcinoma in-situ (DCIS) of breast shows regressive changes in form of tumor attenuation and fibrosis which is further associated with increased invasiveness of disease rather than protective mechanism, as it was proved on immunohistochemistry (IHC) by loss of myoepithelial cells by Chivukula et al. **Aims:** To list the biologic type of DCIS and describe the morphologic spectrum of regressive changes associated with DCIS. To study the association between regression and tumor characteristics like inflammation, extent of disease and hormone receptor profile. **Methods:** A retrospective analysis of 50 cases of DCIS with or without invasive component were retrieved over period of 3 years (Aug 2016 to Aug 2019). Histopathology was reviewed by two pathologists using standard review form which included different parameters like DCIS type, tumor extent of regression, inflammation and extent of disease. The hormone receptor status of all the cases was evaluated using ER, PR and Her2neu by IHC. **Results:** Out of 50 cases, high-grade DCIS was found in 33 cases (66%). The most common stage of regression was stage I (50%) followed by stage II (24%), stage III (2%) and absence of regression in 24% cases. The diffuse lymphocytic infiltration was found in 18% cases and minimal infiltration found in 46% cases. 25% of cases show triple negative hormone receptor response. The most common form of high-grade DCIS (HG-DCIS) was comedo followed by solid and cribriform and least were papillary and micropapillary pattern. **Conclusions:** We conclude that regression was found in 38 (77%) cases with most being in stage I. There is a strong association of HG-DCIS with triple negative receptor profile. However, regression and inflammation did not show any association. No association was found between the extent of disease and regression.

INTRODUCTION

Ductal carcinoma in situ (DCIS) is a proliferation of malignant epithelial cells which are confined to ductolobular system of the breast. It is considered to be a precursor lesion of invasive carcinoma. It can present with or without invasive carcinoma. DCIS is a heterogeneous disease in terms of presentation, morphology, biomarker expression and molecular alterations.[1] Due to increase in screening of women through implementation of mammography, there is exponential increase in the number of patients diagnosed with DCIS. Mammographically, DCIS detected micro-calcification even when no lump is palpable.[2-4] Risk factors for development of DCIS are similar to invasive breast carcinoma which include age, family history, nulliparity, late menopause, elevated BMI etc.[5,6]

On the basis of nuclear grade, DCIS is graded into low, intermediate and high grade. There are many morphological variants of DCIS including comedo, solid, papillary, micropapillary, cribriform, apocrine etc. Nuclear grade and comedo necrosis are important morphologic features for predicting progression and prognosis of DCIS.[7,8]

Tumor regression is continuum of changes leading to fibrosis, obliteration and effacement of neoplastic population in wide spectrum of malignancies like melanoma, prostrate carcinoma, esophageal carcinoma, leucoplakia etc.[9-12] These regressive changes can be due to host immune response in

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attempt to eradicate neoplastic cells or due to neo adjuvant chemotherapy. In some tumors these regressive changes seem to be indicator of poor prognosis. It was earlier described as ‘‘scars’’ in DCIS that were composed of circumferential layers of collagen and elastic tissue by Muir and colleagues in 1934.[13,14] Later, Rosen introduced a process referred toas “healing”, stating that “marked periductal fibrosis can, on occasion, be associated with extensive obliteration of ductal carcinoma in situ (DCIS)”. It was Chivukula who described healing as regressive changes.[15] Later Lee and his colleague’s found association of inflammation with nuclear grade, Her2neu positivity and extent of lesion.[16]

The aim of our study is to list and describe the morphologic spectrum of regressive changes. Also discuss the association between regression and tumor characteristics like inflammation, extent of disease and hormone receptor profile.

MATERIALS AND METHODS

This study was conducted after taking ethics clearance from our institutional ethics committee and as it was retrospective study, clinical details were taken from department records.

The present study is a retrospective hospital based cross sectional study of 50 cases of DCIS with or without invasive component. All the cases over a period of 3 years (Aug 2016 to Aug 2019) were retrieved from the archives of the Department of Pathology at tertiary care centre.

Core biopsies, trucut biopsies, lumpectomy and mastectomy specimens which showed DCIS were included. Cases whose paraffin blocks could not be retrieved and those with incomplete history and follow up were excluded from the study.

Histopathology Review and Diagnostic Classification

The histopathology was reviewed on haematoxylin and eosin (H&E)-stained sections independently by two pathologists using a standard review form which included different parameters like DCIS type, regression, inflammation and extent of disease. The hormone receptor status of all the cases was evaluated.

DCIS was graded as follows:

Grade 1 (Low Grade). The nuclei are monomorphous and 1.5 to 2 times the diameter of a RBC with inconspicuous nucleoli and diffuse chromatin. The nuclei are usually orientated (polarized) toward the lumen.

Grade 2 (Intermediate Grade). The nuclei are intermediate between 1 and 3.

Grade 3 (High Grade). The nuclei are large and pleomorphic, >2.5 times the diameter of a RBC with more than one nucleolus per cell and contain irregular chromatin. The nuclear orientation is usually irregular (nonpolarized).[17-21]

Regressive changes were assessed in each in situ neoplastic gland using criteria previously described by Chivukula et al.

Three stages were defined:

Stage 1: Minimal loss/effacement of neoplastic epithelium and mild periductal fibrosis (≤1.0× the radius of the gland)

Stage 2: Significant loss/effacement of neoplastic epithelium and prominent periductal fibrosis (>1.0× the radius of the gland)

Stage 3: Complete loss of neoplastic epithelium with lumen obliteration and prominent periductal fibrosis (>1.0× the radius of the gland)[15]

The presence of periductal chronic inflammation in each involved gland was assessed in terms of intensity and distribution (Table 1,2)[22]

Morphological variants of DCIS studied were categorized as comedo, solid, cribriform, papillary and micropapillary.

In cases with invasive carcinoma, we recorded tumor size, tumor grade, tumor stage, and status of axillary lymph nodes.

Immunohistochemical Staining and Evaluation

Estrogen receptor (ER), progesterone receptor (PR) immunohistochemical studies were carried out and their results were interpreted according to Allred score and Her2neu IHC staining pattern was also seen.

Statistical Analysis

All the histopathological features and hormone receptor status were analyzed for their frequency. Chi square test with one-degree freedom, wherever applicable, was used to test for associations between histopathological features and categories. P-value of <0.05 was considered significant. Statistical analysis was performed using GraphPad software.

Table 1: Intensity pf periductal chronic inflammation

Intensity mild	**<0.5 x the radius of the gland**
Intensity moderate	0.5-1.0 x the radius of the gland
Intensity severe	>1.0 x the radius of the gland

Table 2: Distribution of periductal chronic inflammation

Distribution focal	**<50% of glands involved**
Distribution diffuse	>50% of glands involved

Table 3: Different stages of regression along with photomicrographs

STAGE I	**Minimal loss/ effacement of neoplastic epithelium**	**Mild periductal fibrosis**	**Fig. 3**
STAGE II	Significant loss/ effacement of neoplastic epithelium	Prominent periductal fibrosis	Fig. 4

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STAGE III	Complete loss/ effacement of neoplastic epithelium	Prominent periductal fibrosis	Fig. 5

Table 4: Association between grade of DCIS and different patterns of DCIS

	Comedo	Solid	Cribriform	Micropapillary	Papillary
Low	0	1	2	0	4
Intermediate	4	1	2	1	2
High	14	8	6	5	0

Table 5: Association of different histological parameters and IHC markers with stages of regression

S No..	Parameters	Regression				P value
1.	DCIS Grade	Stage 0	Stage I	Stage II	Stage III	0.293
	Low	4	3	0	0	
	Intermediate	4	4	3	0	
	High	4	18	9	1	
2.	Inflammation intensity					0.159
	No	1	0	0	0	
	Mild	8	12	3	0	
	Moderate	3	9	5	0	
	Severe	0	4	4	1	
3.	Extent of disease					0.527
	Stage 0	3	4	0	0	
	Stage I	3	10	6	0	
	Stage II	3	5	3	0	
	Stage III	3	6	3	1	
4.	ER status					0.018
	Positive	11	9	5	0	
	Negative	1	16	7	1	
5.	PR status					0.009
	Positive	11	9	5	0	
	Negative	1	16	7	1	
6.	Her2neu					0.008
	Positive	6	1	2	0	
	Equivocal	2	11	1	1	
	Negative	4	13	9	0	

RESULTS

A total of 50 cases were studied over the duration of 3 years. The mean age of patients was 45 years (18-80 years).60 % of DCIS were in 30-50 years age group [Fig. 1]. Among all the DCIS studied, high grade DCIS (HG DCIS) were found in 33 cases (66%), rest were low and intermediate grade. Regression was found in 77% cases with most cases being in stage I which was 25 (50%) cases (Fig.2). Table 3 shows different stages of regression around DCIS. Among different DCIS types most common type was comedo pattern in 18 (36%) cases, next common was solid and cribriform, both of which were found in 10 cases (20%) each and least were micropapillary and papillary pattern which were in 6 cases (12%) each (Table 4).

Histopathological features of these 50 cases were assessed systematically based on the review form and on immunohistochemistry by two pathologists (Table 5). Severe degree of inflammation was found in stage I and stage II regression (Fig. 6)

Pure DCIS were found in 7 cases (14%). Rest of the DCIS were seen in association with invasive carcinoma. IHC was applied on all 50 cases of DCIS with or without invasive component. ER and PR both were found positive in 25 cases (50%) and rest were negative. Her2neu were found positive in 9 cases, negative in 26 cases and remaining results were equivocal which can be decided by FISH only.

Among all the parameters, in our study we found hormone receptor status were significantly associated with regression where P value <0.05.

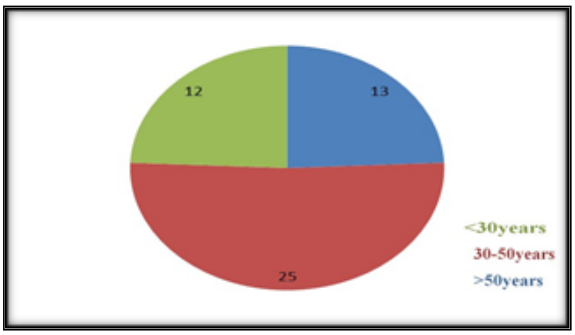

Figure 1: Pie diagram showing age distribution of DCIS cases

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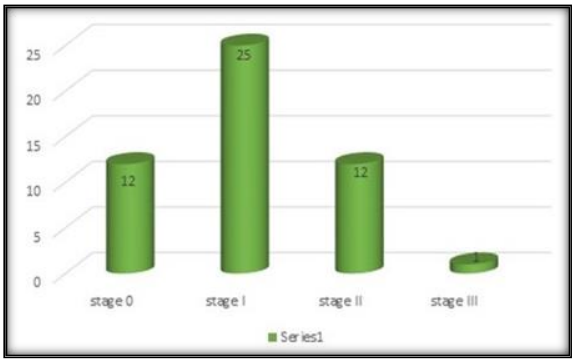

Figure 2: Showing distribution of cases according to the stage of regression.

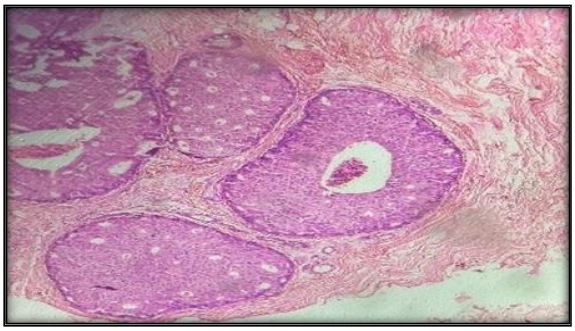

Figure 3: Microphotograph showing mild periductal fibrosis with minimal effacement of neoplastic epithelium.(HE 10x)

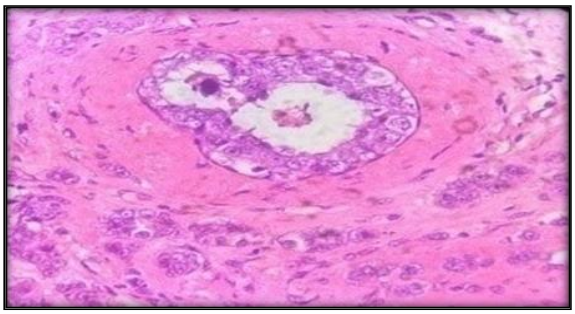

Figure 4: Microphotograph showing prominent periductal fibrosis with significant effacement of neoplastic epithelium. (HE 10x)

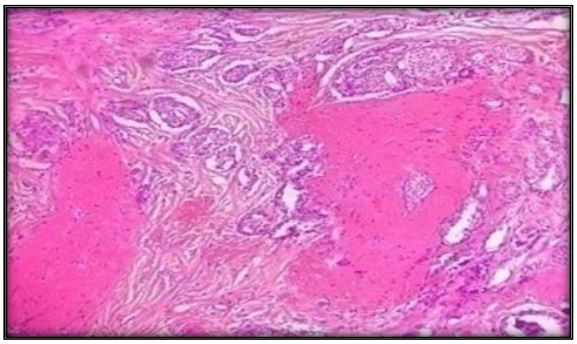

Figure 5: Microphotograph showing prominent periductal fibrosis with complete effacement of neoplastic epithelium.(HE10x)

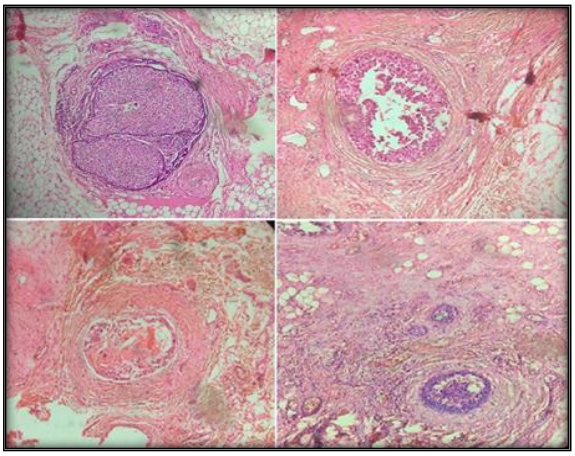

Figure 6: Microphotograph showing distribution of periductal chronic inflammation and stage of regression upper left stage I, upper right stage II lower left stage III and lower right stage III. (HE10x)

DISCUSSION

Ductal carcinoma in situ of the breast is a heterogeneous group of lesions with a wide morphologic spectrum and biologic behavior. 80-85% DCIS are detected on mammography during screening. Nuclear grade and comedo necrosis are important morphologic features for predicting the progression and prognosis in DCIS. Tumor regression has been studied and documented in certain malignancies like melanoma, esophageal carcinoma, neuroblastoma etc., yet it's not completely understood. Regressive changes in form of fibrosis, hyalinization and inflammation were earlier considered as healing process but later on Chivukula described it as a biologic change leading to invasive carcinoma with greater regressive changes leading to much worse prognosis.

Regression was found in 77% of cases with most showing stage I regression. There is a strong association of hormone receptor profile with different stages of regression as has been proposed by Wasserman et al. However, no association between regression and inflammation was seen in our study. No association was found between the extent of disease and regression. We agree that there is some alteration in the lineage specific markers by the inflammatory cells which also alters the myoepithelial cell response in cases with more regressive changes leading in progression to invasive carcinoma. However, why such regressive changes are also seen in periductal mastitis, ductal papilloma and fibrocystic disease needs to be explained.

Chivukula M et al, 2009 studied 59 cases of HGDCIS and found regressive changes as a distinct biologic phenotype with more aggressive behavior and loss of expression of myoepithelial cells and have suggested that immune response leading to tumor regression may act as a trigger to more aggressive disease by altering the myoepithelial layer and promoting stromal invasion similar to that seen in cellular rejection.[15]

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Wasserman JK et al, 2015 studied 51 cases and found that regressive changes were frequent in HGDCIS and concluded that advanced regressive changes and inflammation are frequent in hormone negative lesions.[22]

Morita et al, 2016 studied the association between spontaneous healing and TIL (tumor infiltrating lymphocytes) in patients with DCIS and found that there was strong association between spontaneous healing and high TILs.[23]

Denkertet al,2010reported a strong association between TIL and chemotherapy response in invasive breast cancers.[24] As chemotherapeutic agents release tumor associated antigens which trigger immune response which is strong in those conditions where already immune system is sensitized and thus this increased immune response led to pathologic complete response (pCR).[25-28]

It has been found that there is more neoductogenesis with high volume of HGDCIS or invasive carcinoma on subsequent lumpectomy signifying a further tumor stromal response by myoepithelial cells.[29]

The limitation of our study was small sample size, no myoepithelial marker was applied. Extended study needs to be done on tumor microenvironment and epithelial stromal interface to understand the reason for higher regressive changes progressing to invasive carcinoma.

CONCLUSION

DCIS is a very complex and heterogeneous disease, therefore its biology is still not well understood. It varies with grade, hormonal status and genetic factors. We concluded that in HGDCIS, stage I regression is most often seen and had an association with triple negative hormone status. In HGDCIS the most common pattern is comedo type and is strongly associated with regression. Microenvironment of DCIS plays an important part for its progression to invasive carcinoma. However, much needs to be worked up on immune response by TILs and its association with chemotherapy response.

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