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Morphological and Immunohistochemical Features of Chronic Inflammation in the Breast

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Abstract Chronic inflammatory breast lesions are diagnostically challenging because they may mimic neoplastic disease and overlap with age-related tissue remodeling. Objective: To characterize the morphological and immunohistochemical features of chronic breast inflammation and assess their relationship to proliferative activity, local immune response, and cell-cycle regulation. Methods: The study included 63 breast tissue specimens: 13 morphologically normal controls and 50 cases of chronic inflammation. Histology, histochemistry, morphometry, and immunohistochemistry for Ki-67, CD45, and p53 were performed. Results: Chronic inflammation was associated with lymphoplasmacytic infiltration, stromal fibrosis, distortion of ductolobular structures, and reactive epithelial changes. Histochemistry demonstrated connective tissue remodeling and collagen condensation. Immunohistochemically, chronic inflammation showed lower Ki-67 expression, markedly higher CD45 expression, and no sharp increase in p53 compared with normal tissue. Conclusions: Chronic breast inflammation is characterized by coordinated epithelial, stromal, and immune-cellular remodeling. Combined morphological and immunohistochemical assessment improves the differential interpretation of biopsy and operative material and helps distinguish chronic inflammation from age-related involution.

Keywords Breast, Chronic inflammation, Pathology, Histochemistry, Morphometry, Immunohistochemistry, Ki-67, CD45, p53, Fibrosis, Tissue remodeling

1. Introduction

Chronic inflammatory processes of the breast occupy an intermediate diagnostic position between purely reactive lesions and tissue changes that may simulate tumor-like growth. [1,4,5] In routine pathology practice, these lesions are challenging because stromal sclerosis, lymphoplasmacytic infiltration, architectural distortion, epithelial reactivity, and focal macrophage-rich areas may mimic proliferative or even neoplastic processes on both imaging and histologic examination. [14,15,16]

To address this diagnostic challenge, the present study integrates routine microscopy with histochemistry, cytomorphometry, digital morphometry, and immunohistochemistry. [2] From a morphobiological perspective, chronic inflammation should not be regarded as a simple infiltrative event. Rather, it represents a prolonged and spatially heterogeneous remodeling process involving epithelial injury and repair, extracellular matrix reorganization, microcirculatory alterations, and a persistent local immune response. [3,6,17]

This issue is relevant not only to the diagnosis of benign breast disease but also to the broader pathology of tissue remodeling associated with carcinogenesis-related microenvironments. Sustained inflammation may create a biologically active tissue background characterized by cytokine signaling, matrix remodeling, and altered balance between proliferation and regeneration. At the same time, chronic inflammatory lesions should not be interpreted as direct evidence of malignant transformation. [7,8,9] Careful morphologic and immunohistochemical evaluation is therefore required to avoid both underdiagnosis and overdiagnosis. [12]

The aim of the present study was to characterize chronic inflammatory lesions of the breast with particular emphasis on histologic architecture, histochemical matrix alterations, representative morphometric patterns, and the expression profiles of Ki-67, CD45, and p53. [10,13]

2. Materials and Methods

This comparative descriptive-analytical study was performed on breast tissue specimens obtained from biopsy

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material, surgical samples, and archival paraffin blocks. The total study cohort comprised 63 cases, including 13 morphologically normal or near-normal control specimens and 50 cases with clinicopathologically verified chronic inflammatory processes of the breast.

To account for the confounding effect of age-related involution, the material was stratified into two age groups: 30–35 years and 35–65 years. The primary comparative statistical analysis was focused on the 30–35-year subgroup, as this interval minimized involutional and hormonal influences and allowed a more accurate interpretation of inflammation-associated epithelial and stromal alterations. The 35–65-year subgroup was used for descriptive analysis of age-related changes.

Inclusion in the chronic inflammation group required histologic confirmation of chronic inflammatory changes in diagnostically adequate tissue. Histologic criteria included lymphoplasmacytic infiltration, stromal fibrosis or sclerosis, remodeling of ductolobular structures, reactive epithelial changes, and, in some cases, macrophage-rich or granulomatous components. Control specimens showed no evidence of inflammation, atypia, proliferative disease, or neoplastic growth. Exclusion criteria comprised acute purulent inflammation, extensive necrosis, carcinoma in situ, invasive carcinoma, pronounced atypical proliferative lesions, poor fixation, severe autolysis, and insufficient tissue preservation.

Specimens were fixed in 10% neutral buffered formalin, routinely processed into paraffin, and sectioned at 3–5 μm. Hematoxylin and eosin staining was used for general morphological evaluation. The periodic acid–Schiff (PAS) reaction was applied to assess basement membrane integrity and carbohydrate-rich components. Van Gieson staining was used to evaluate collagen deposition, stromal density, and fibrotic remodeling.

Table 1. Study cohort and diagnostic grouping

Group	Number of cases	Comment
Morphologically normal control	13	No inflammation, atypia, or neoplastic growth
Chronic inflammatory lesions	50	Clinicopathologically verified chronic inflammatory changes
Total	63	Biopsy, operative, and archival paraffin material

Table 2. Age distribution of the study cohort

Group	30-35 years	35-65 years	Total
Control	12	1	13
Chronic inflammation	25	25	50
Total	37	26	63

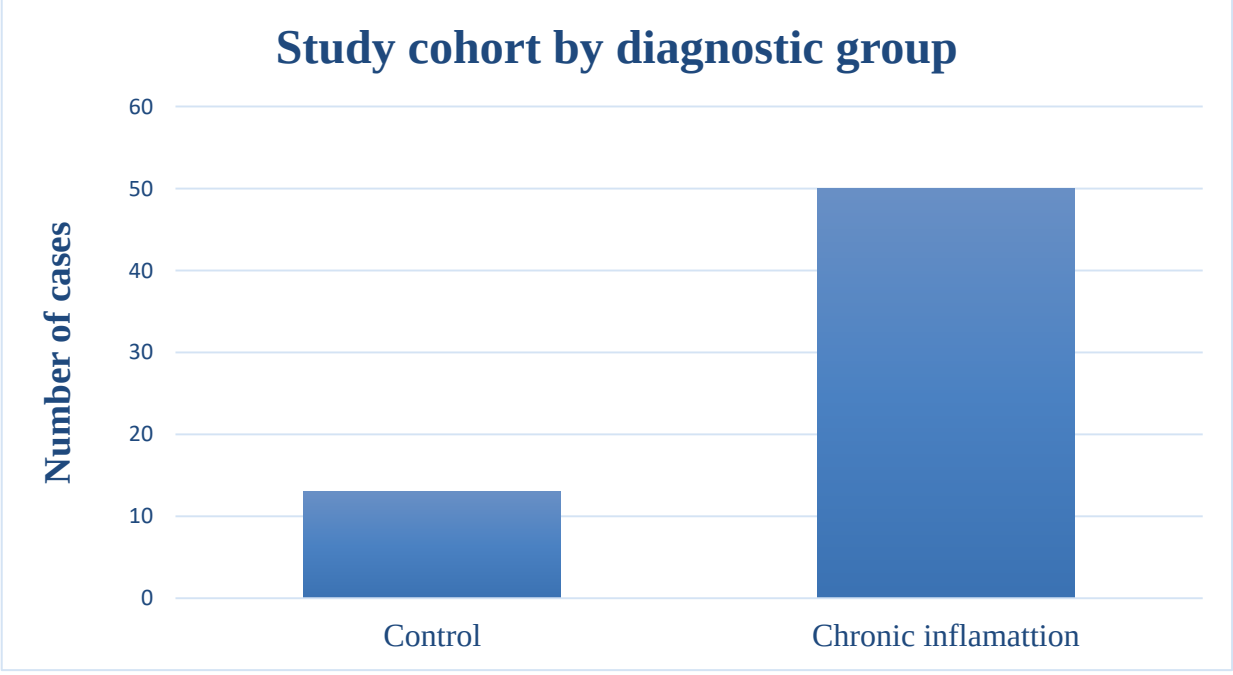

Figure 1. Distribution of the study cohort by diagnostic group

Morphometric and cytomorphometric analyses included epithelial cell number per field, cell size, nuclear size, nuclear–cytoplasmic ratio, mitotic index, apoptotic index, stromal proportion, fibrosis-related changes, and inflammatory infiltrate density in representative fields. Digital analysis of selected morphometric and immunohistochemical parameters was performed using QuPath 0.5.1 in representative regions after exclusion of artifacts, folds, nonspecific staining, necrotic areas, and non-diagnostic regions.

Immunohistochemical analysis was performed on paraffin sections using Ki-67 as a marker of proliferative activity, CD45 as a marker of leukocytic inflammatory infiltration, and p53 as an indicator of cell-cycle regulation and stress-related nuclear response. Evaluation included assessment of localization, intensity, distribution, and proportion of positive cells. For Ki-67, the percentage of positively stained epithelial nuclei was used as the primary measure of proliferative activity; for CD45, the density and distribution of positive inflammatory cells in stromal, periductal, and perilobular regions were assessed; for p53, nuclear positivity and the extent of positive-cell distribution were evaluated in the context of overall tissue morphology.

Quantitative data were expressed as mean ± standard error for normally distributed variables and as median with interquartile range for non-normally distributed data. Group comparisons were performed using Student's t-test or the Mann–Whitney U test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. A p value < 0.05 was considered statistically significant.

Table 3. Representative morphometric values in morphologically normal breast tissue

Parameter	32-year observation	61-year observation
Epithelial cells per field	121 ±2.1	80 ±10
Cell diameter, μm	17.5 ±1.2	15.6 ±1.3
Nuclear diameter, μm	6.3 ±0.5	5.4 ±0.4
Nuclear-cytoplasmic ratio	0.33 ±0.03	0.32 ±0.02
Mitotic index, %	0.9 ±0.2	0.5 ±0.1
Apoptotic index, %	1.2 ±0.3	1.5 ±0.2

Table 4. Immunohistochemical marker expression in normal breast tissue and chronic inflammation

Marker	Normal, 34 years (%)	Normal, 63 years (%)	Chronic inflammation, 34 years (%)	Chronic inflammation, 63 years (%)
Ki-67	10.82	9.12	5.34	4.48
CD45	7.61	9.98	21.97	23.65
p53	11.40	9.77	2.20	3.80

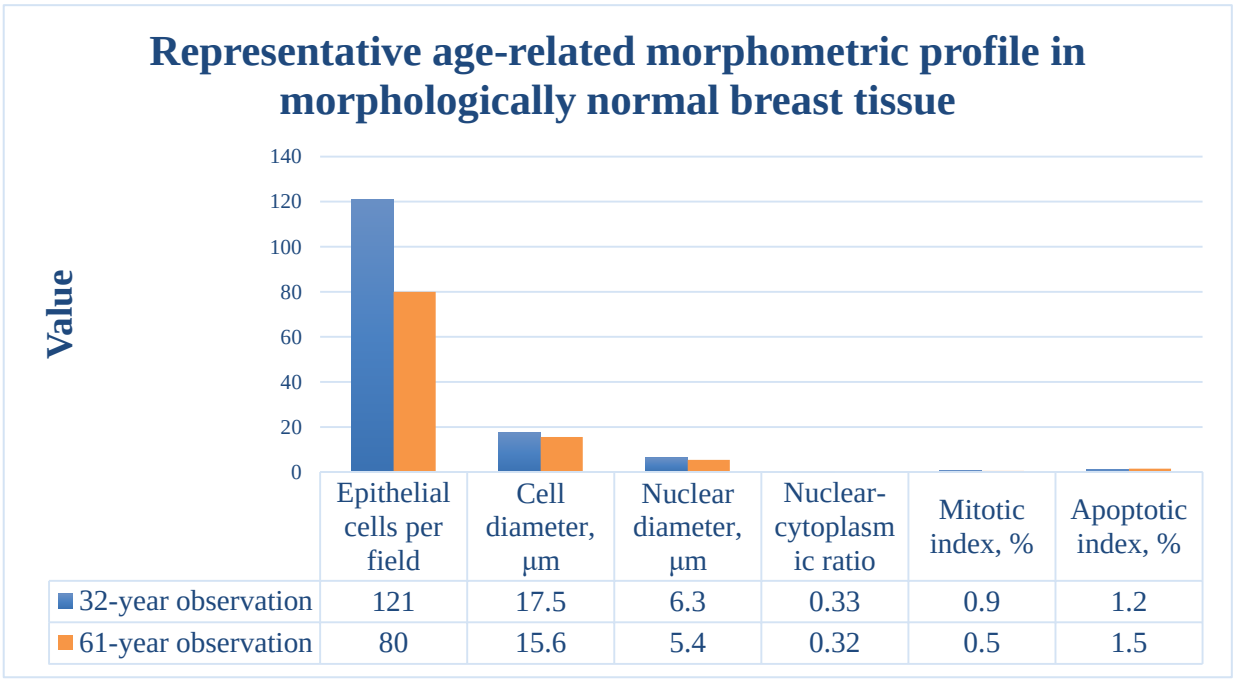

Figure 2. Representative age-related morphometric profile in morphologically normal breast tissue

3. Results

A total of 63 cases were analyzed, including 13 controls and 50 chronic inflammatory lesions. Twelve of the 13 control cases belonged to the 30-35-year age group, whereas one control case and 25 chronic inflammatory cases belonged to the 35-65-year age group. Accordingly, the principal comparative design emphasized the younger age stratum, while the older cases provided an additional descriptive framework for assessing the interaction between chronic inflammation and involutional change.

Routine histology showed that morphologically normal breast tissue preserved ductolobular architecture, orderly epithelial arrangement, intact basement membranes, and the absence of significant inflammatory infiltrates. With increasing age in the control material, a physiological involutional trend was evident, including reduced epithelial cellularity, relative expansion of the stromal component, and denser collagen organization, but without destructive, dysplastic, or clearly proliferative alterations.

By contrast, chronic inflammatory lesions demonstrated persistent mononuclear infiltration dominated by lymphocytes and plasma cells, frequently accompanied by macrophages. The stromal compartment showed fibrosis and sclerosis of varying degree, while ductal and lobular units displayed partial distortion, reactive epithelial swelling, dystrophic change, or local remodeling. In some areas, perivascular and periductal infiltration was evident, and in selected cases the tissue pattern suggested macrophage-rich or granulomatous chronic inflammation rather than acute destructive disease.

Histochemically, chronic inflammation was accompanied by a less uniform distribution of PAS-positive material in epithelial cytoplasm, ductal walls, and basement membrane zones, suggesting altered secretory-intercellular composition and active reparative remodeling. Van Gieson staining demonstrated increased collagen density and condensation in stromal areas, supporting the interpretation that chronic inflammation in the breast is not merely infiltrative but also fibrosing and matrix-remodeling in nature.

Table 5. Integrative interpretation of the main pathological patterns

Domain	Morphologically normal tissue	Chronic inflammation	Diagnostic implication
Architecture	Preserved ductolobular structure	Partial distortion and remodeling of ductolobular units	Supports distinction between physiological structure and chronic injury-related remodeling
Inflammatory component	Absent or minimal	Persistent lymphoplasmacytic infiltrate, sometimes macrophage-rich	Favors chronic inflammatory lesion
Stroma	Age-related involutional increase possible	Fibrosis, sclerosis, collagen condensation	Highlights fibroproductive nature of chronic inflammation
Epithelial state	Ordered, low physiologic turnover	Reactive change, variable dystrophy, adaptive remodeling	Requires correlation with Ki-67 and morphology
IHC profile	Lower CD45, higher physiologic Ki-67 in younger control	High CD45, reduced Ki-67, no sharp p53 rise	Useful for differential interpretation of equivocal biopsies

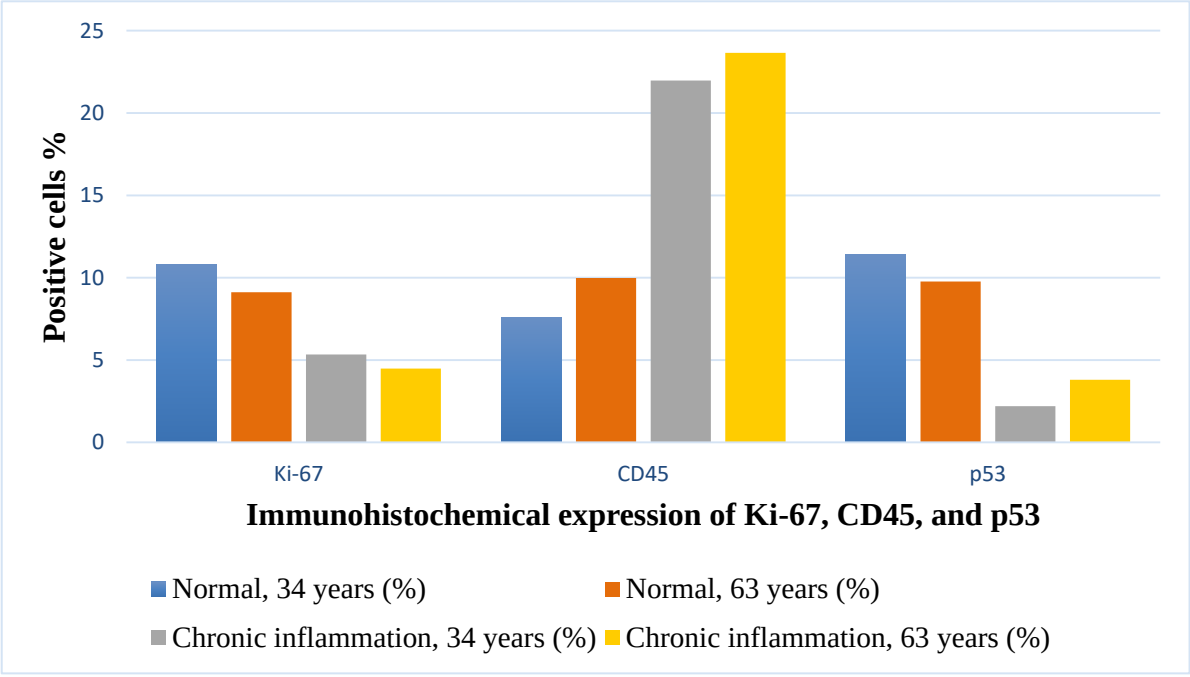

Figure 3. Comparative immunohistochemically expression of Ki-67, CD45, and p53 in normal breast tissue and chronic inflammation

Representative morphometric observations in morphologically normal tissue revealed an age-dependent decline in epithelial cellularity and proliferation-associated features. The number of epithelial cells per field decreased from 121 ± 2.1 in the 32-year representative case to 80 ± 10 in the 61-year representative case. Cell diameter declined from 17.5 ± 1.2 μm to 15.6 ± 1.3 μm, and nuclear diameter from 6.3 ± 0.5 μm to 5.4 ± 0.4 μm. The nuclear-cytoplasmic ratio remained relatively stable (0.33 ± 0.03 vs 0.32 ± 0.02), whereas the mitotic index decreased from 0.9 ± 0.2% to 0.5 ± 0.1%, and the apoptotic index modestly increased from 1.2 ± 0.3% to 1.5 ± 0.2%. These observations support the notion that age-related involution alters cellular density and turnover even in the absence of inflammation.

Cytomorphometrically, chronic inflammation was associated with greater variability in epithelial cell size and nuclear dimensions, mild anisocytosis and anisokaryosis, localized shifts in the nuclear-cytoplasmic ratio, and reactive-adaptive changes rather than overt neoplastic atypia. Inflammatory -cell accumulation and stromal fibroblast prominence were more evident in chronically inflamed tissue, consistent with ongoing repair and fibrosis.

Immunohistochemical analysis demonstrated a coherent but non-uniform profile. Ki-67 expression was lower in chronically inflamed tissue than in morphologically normal breast tissue in both younger and older representative cases, indicating reduced proliferative activity of epithelial cells under chronic inflammatory conditions. CD45 expression was substantially increased in chronic inflammation, confirming intensified local leukocytic infiltration and a sustained immune-cellular response. p53 expression did not show a sharp rise in chronic inflammatory lesions and remained low to moderate, which argues against dominant overt dysregulation in the analyzed material.

4. Discussion

The present analysis supports the view that chronic breast inflammation should be interpreted as a complex morphobiological process combining persistent inflammatory activity, reparative remodeling, epithelial adaptation, and progressive stromal fibrosis. This interpretation is important because the histologic appearance of chronic inflammatory lesions may overlap both with involutional changes and with lesions that raise concern for neoplasia.

One of the central findings of the study is the distinction between inflammation-related remodeling and physiologic involution. In morphologically normal tissue, aging was associated primarily with reduced epithelial cellularity and functional activity, accompanied by relative stromal expansion. In chronic inflammation, however, the remodeling pattern included persistent mononuclear infiltration, fibrosclerosis, reorganization of ductolobular units, and a more heterogeneous cytomorphometric profile. These observations indicate that age alone cannot account for the architectural and cellular alterations seen in inflamed tissue.

The histochemical findings further refine this distinction. Redistribution of PAS-positive material and increased collagen condensation on Van Gieson staining indicate that chronic inflammation is accompanied by matrix-level and basement membrane-associated alterations. These changes are consistent with a tissue microenvironment in which injury, repair, fibrosis, and altered epithelial-stromal interaction occur simultaneously. From a diagnostic perspective, such findings may be misinterpreted if evaluation relies on routine histology alone, particularly in small biopsy specimens.

The immunohistochemical profile adds an additional biologically coherent layer of interpretation. Lower Ki-67 expression in chronically inflamed tissue suggests that the dominant process in these lesions is not excessive epithelial proliferation, but rather structural remodeling with limited regenerative turnover. This observation is of particular importance because reactive lesions might be expected to show increased proliferative activity, whereas the present data indicate that prolonged inflammation may instead be associated with a constrained proliferative state.

By contrast, markedly increased CD45 expression confirms that chronic inflammatory lesions remain immunologically active even when epithelial proliferation is relatively low. The combination of reduced Ki-67 and increased CD45 represents one of the most informative patterns identified in the study. This profile helps distinguish chronic inflammatory lesions from processes in which epithelial expansion is the dominant morphologic feature and underscores the diagnostic importance of evaluating inflammatory-cell architecture in addition to epithelial morphology.

The p53 findings require cautious interpretation. In the analyzed material, p53 expression did not show a marked increase in chronic inflammatory lesions. This does not exclude stress-related signaling or localized regulatory disturbances, but it suggests that widespread overt p53-associated dysregulation was not a dominant feature in the studied cases. Accordingly, p53 should be regarded as a contextual marker that is most informative when interpreted in conjunction with morphologic and proliferative features rather than as an isolated indicator of preneoplastic transformation.

Taken together, these findings support a practical diagnostic approach to chronic breast inflammation. First, the overall architecture and inflammatory pattern should be assessed on routine histology. Second, matrix remodeling and fibrosis should be further characterized using histochemical methods. Third, morphometric and cytomorphometric parameters, when available, may help objectify epithelial and stromal alterations. Fourth, a focused immunohistochemical panel including Ki-67, CD45, and p53 may be applied in diagnostically difficult cases. Such a layered approach may improve the standardization of pathology reporting and reduce interpretive ambiguity in biopsy and operative material.

5. Conclusions

Chronic inflammatory processes in the breast are characterized

by a reproducible constellation of pathomorphological changes, including mononuclear inflammatory infiltration, stromal fibrosis and sclerosis, architectural remodeling of ductolobular units, and reactive epithelial alterations.

Histochemical techniques, particularly the periodic acid–Schiff (PAS) reaction and Van Gieson staining, provide diagnostically valuable information on basement membrane-associated changes, connective tissue remodeling, and collagen condensation, thereby complementing routine histologic evaluation.

Morphometric and cytomorphometric analyses facilitate differentiation between inflammation-related remodeling and age-associated involution by objectively assessing epithelial cellularity, nuclear parameters, proliferative–apoptotic balance, and structural variability.

The immunohistochemical profile characterized by reduced Ki-67 expression, increased CD45 expression, and the absence of marked p53 elevation supports the interpretation of chronic inflammation as a process dominated by immune -cellular activation and tissue remodeling rather than by overt dysregulated epithelial proliferation.

An integrated morphological approach is therefore recommended for the differential diagnosis of chronic inflammatory breast lesions in biopsy and surgical specimens, particularly in cases where clinical or radiologic findings raise concern for neoplasia.

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