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The Role of Transcription Factor NF-κβ In Pathogenesis of Invasive Breast Cancer

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Abstract: Nuclear Factor-κβ (NF-κβ) is a key molecule involved in regulating inflammation, immune responses, and cancer progression. Its role in invasive breast cancer has become an important focus in recent research due to its influence on tumor growth, survival, and spread. This review examines the value of NF-κβ as an immunohistochemical marker in breast cancer diagnosis and prognosis. We explore how NF-κβ expression in breast cancer tissues is linked to clinical and pathological factors such as tumor size, grade, lymph node involvement, hormone receptor status, and patient survival outcomes. Additionally, the review discusses the potential of NF-κβ to predict responses to treatment, particularly chemotherapy and targeted therapies. By analyzing existing studies, we provide insights into how NF-κβ functions both to promote and, in some cases, suppress tumor activity, reflecting its complex role in cancer biology. This review emphasizes the potential of NF-κβ as a valuable biomarker for guiding breast cancer management while highlighting the need for further research to better define its clinical utility and standardize its assessment.

Keywords: *Nuclear Factor-κβ, Breast Cancer*

Introduction.

Invasive breast cancer, also referred to as infiltrating breast cancer, is a malignant condition in which cancer cells breach the normal confines of the milk ducts or lobules of the breast tissue and infiltrate the surrounding stromal tissues. This invasion marks the transition from localized in situ lesions, such as ductal carcinoma in situ (DCIS), to a more advanced and potentially metastatic state. Understanding the pathological changes and mechanisms underlying this progression is crucial for effective clinical management and therapeutic decision-making [1].

Invasive breast cancer is broadly classified into molecular subtypes based on receptor expression profiles: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). These subtypes include luminal A (ER/PR positive, HER2 negative, low proliferation), luminal B (ER positive, often HER2 positive or high proliferation), HER2-enriched (HER2 positive, ER/PR negative), and triple-negative breast cancer (TNBC) (ER/PR negative, HER2 negative). Each subtype is associated with distinct biological behaviors, clinical outcomes, and responses to treatment, necessitating tailored therapeutic approaches [1].

The molecular landscape of invasive breast cancer often features mutations in key genes such as TP53, PIK3CA, and BRCA1/2. These mutations drive oncogenesis through disruption of cellular homeostasis, proliferation control, and DNA repair mechanisms. Epigenetic changes, such as methylation of tumor suppressor gene promoters, and aberrations in signaling pathways, including PI3K/AKT and MAPK, further contribute to tumor initiation and progression [2].

Histological Types

Invasive Ductal Carcinoma (IDC): IDC represents the most prevalent histological type, accounting for approximately 70-80% of all invasive breast cancers. It arises from the epithelial lining of the milk ducts and typically forms a stellate mass on gross examination. Microscopically, IDC exhibits varying degrees of glandular differentiation, nuclear atypia, and mitotic activity. The heterogeneity in IDC poses challenges for prognostication and underscores the importance of individualized treatment strategies [3].

Invasive Lobular Carcinoma (ILC): ILC constitutes 10-15% of invasive breast cancers and arises from the lobules. It is characterized histologically by small, discohesive tumor cells infiltrating in single-file patterns due to loss of E-cadherin expression. ILC often eludes detection on standard imaging modalities due to its diffuse growth pattern, necessitating advanced imaging techniques for accurate diagnosis [4].

Diagnostic Tools

Imaging Techniques: The diagnostic pathway for invasive breast cancer typically begins with mammography, which identifies suspicious calcifications or masses. Ultrasound complements mammography by delineating solid from cystic lesions. In complex cases, magnetic resonance imaging (MRI) provides superior sensitivity, particularly in patients with dense breast tissue, high-risk profiles, or equivocal findings on conventional imaging [5].

Biopsy: Core needle biopsy remains the cornerstone for definitive diagnosis. This procedure not only confirms malignancy but also allows for histopathological assessment and immunohistochemical (IHC) profiling of hormone receptors and HER2 status. IHC findings guide therapeutic decisions and stratify patients into appropriate treatment regimens [6].

Prognostic Factors

Tumor Grade and Stage: Tumor grading assesses differentiation levels, with higher grades indicating poorly differentiated, more aggressive cancers. The Nottingham grading system evaluates tubular formation, nuclear pleomorphism, and mitotic count to assign a grade. Staging incorporates tumor size (T), nodal involvement (N), and distant metastasis (M), as defined by the TNM classification system. Together, grade and stage form critical determinants of prognosis and treatment planning [7].

Lymph Node Involvement: The presence of cancer cells in regional lymph nodes, particularly axillary nodes, significantly impacts prognosis. Sentinel lymph node biopsy (SLNB) is a minimally invasive procedure that identifies nodal metastasis and informs decisions regarding axillary dissection and adjuvant therapies [8].

Treatment Modalities

Surgical intervention remains the primary treatment for localized invasive breast cancer. Options include breast-conserving surgery (lumpectomy), which aims to excise the tumor with clear margins, and mastectomy, which involves complete removal of the breast tissue. Reconstruction options are available for cosmetic restoration. SLNB is frequently performed alongside surgery to assess nodal involvement and reduce unnecessary axillary dissection [9].

Radiotherapy is an integral part of adjuvant treatment, especially after breast-conserving surgery. It targets residual microscopic disease, reducing the risk of local recurrence. Advances in radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), allow for precise delivery while minimizing damage to surrounding tissues [10].

Systemic treatments are guided by molecular subtype and include endocrine therapy for hormone receptor-positive cancers, HER2-targeted therapies (e.g., trastuzumab) for HER2-positive subtypes, and chemotherapy for high-risk or TNBC cases. These therapies address micrometastatic disease and improve overall survival rates [11].

Immune checkpoint inhibitors, such as pembrolizumab, have gained traction in the management of TNBC, which is often immunologically "cold." By inhibiting PD-1/PD-L1 pathways, these agents enhance T-cell-mediated tumor eradication. Ongoing trials are exploring combinations of immunotherapy with other modalities to maximize efficacy [12].

Advances in genomic profiling have enabled precision medicine approaches. Tests like Oncotype DX and MammaPrint stratify patients by recurrence risk and guide the use of adjuvant chemotherapy. Targeted agents, such as PARP inhibitors, exploit synthetic lethality in BRCA-mutated cancers, offering a tailored therapeutic approach [13].

Nuclear Factor-κβ (NF-κβ) is a transcription factor that plays a critical role in regulating immune responses, inflammation, and cell survival. Its aberrant expression has been implicated in various cancers, including invasive breast cancer (IBC). This article explores the role of NF-

κβ in IBC and its association with clinico-pathological variables, with a particular focus on immunohistochemistry and pathological correlations.

Morphological Variants of Invasive BC

I. Invasive Ductal Carcinoma

Invasive ductal carcinoma (IDC) is a neoplastic proliferation and microinvasion of luminal epithelial cells into surrounding breast stroma, by passage through the ductal wall [14]. It involves a progressive loss in basal layer integrity [15]. IDC is the most common histological subtype of malignant breast cancer (BC), accounting for 70–80% of all invasive BCs [16] and 85% of all male breast cancers [17]. IDC may develop from high-grade ductal carcinoma in situ (DCIS) lesions, which are pre-malignant epithelial proliferations, but this progression is not mandatory [18].

Based on histological properties, several subtypes of IDC have been described, including the classical nonspecific subtype/not otherwise specified subtype (IDC-NST/IDC-NOS), breast invasive apocrine carcinoma (BAC), medullary carcinoma of the breast (MBC), mucinous carcinoma/colloid carcinoma (MCB), invasive papillary carcinoma (IPC), invasive micropapillary carcinoma (IMPC), and tubular ductal carcinoma (TC) [19]. IDCs are synthetically classified as “no special type” because these tumors lack sufficient morphological characteristics to be classified as distinct histological types [20].

Clinically, IDC presents as a painless breast lump or other suspicious symptoms, with diagnosis based on clinical assessment, radiological imaging, and tissue biopsy [21]. Less common presentations include skin retraction, nipple discharge, nipple inversion, or changes in breast size, shape, or skin texture [22].

Microscopically, tumor cells may be arranged in cords, clusters, and trabeculae, as shown in Figure 1 [23]. Some tumors exhibit a predominantly solid or syncytial infiltrative pattern with minimal associated stroma [24]. Occasionally, areas mimic invasive lobular carcinoma but lack its distinct cytomorphological characteristics [25].

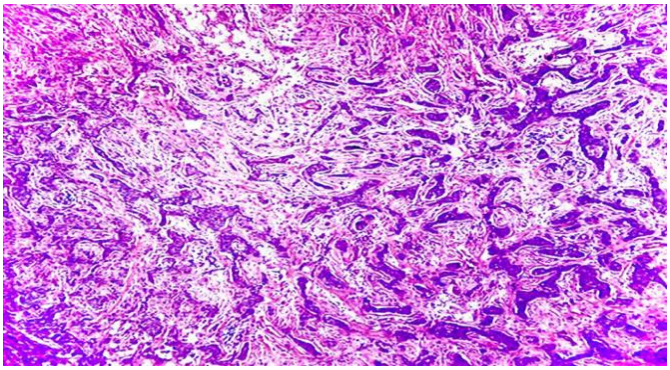

Figure 1: Invasive ductal carcinoma NST with sheets of cells with pleomorphic nuclei and frequent mitosis [23].

Foci of associated DCIS are present in up to 80% of cases [26]. Stromal components vary, ranging from highly cellular fibroblastic proliferation to scant connective tissue or marked hyalinization [27]. Rare cases show lymphoplasmacytoid infiltrate [28]. To be classified as NST, the nonspecialized pattern must constitute >50% of the tumor mass [29].

Rare morphological variants of NST carcinoma include oncocytic, lipid-rich, glycogen-rich, clear cell, sebaceous carcinomas, and those with choriocarcinomatous, pleomorphic, melanocytic features, or osteoclast-like stromal giant cells [30].

Invasive breast carcinoma with medullary pattern now represents one end of the spectrum of TIL-rich IBC-NST, proposed as "IBC-NST with medullary pattern" [23].

Pleomorphic carcinoma, a rare variant of high-grade NST carcinoma, is characterized by bizarre, multinucleated tumor giant cells comprising >50% of the tumor cells [26]. Carcinoma with osteoclast-like stromal giant cells involves inflammatory, fibroblastic, hypervascular stroma with extravasated erythrocytes and lymphocytes [31].

IDC prognosis depends on disease stage and biomarker expression. Methods like the Nottingham Prognostic Index (NPI) assist in predicting outcomes and supporting clinical decisions [29].

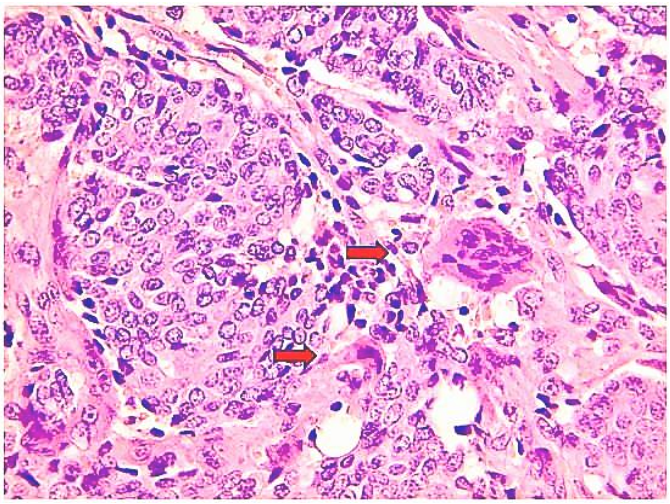

Figure (2): H &E stain 40× showing invasive ductal carcinoma with at least 2 osteoclast-like giant cells [29].

II. Special Types of Invasive Breast Cancer

1. Tubular Carcinoma

A special type of well-differentiated invasive carcinoma composed almost completely of tubules [31] accounts for ~1–4% of all invasive BCs [32]. Approximately 60–70% present as non-palpable, mammographically detected lesions and are more common in women in their sixth or seventh decade who are undergoing breast cancer screening [33].

Microscopically, tubular carcinoma predominates with tubules composed of a single layer of epithelial cells with open lumens. The tubules are arranged haphazardly; are generally oval, rounded, and angulated in shape; and lack peripheral myoepithelial cells. The cells are small to moderate in size, regular with little nuclear pleomorphism, inconspicuous nucleoli, and scanty mitotic figures, as shown in Figure 3 [34].

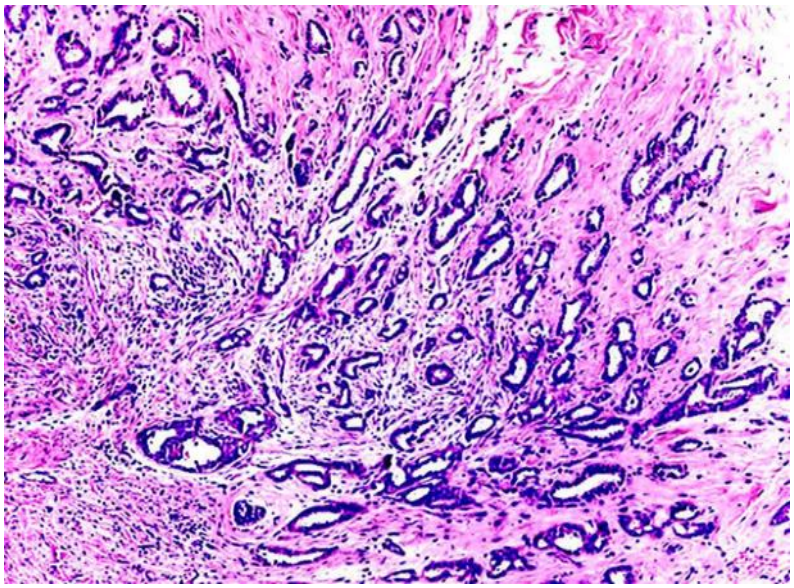

Figure (3): Tubular carcinoma showing bland-looking tumor cells arranged in tubules with patent lumens. Myoepithelial cells are absent, and the malignant tubules are arranged in an irregular stellate pattern. The intervening stroma is densely fibrotic [35].

A consistent feature of tubular carcinoma, particularly useful on needle core biopsy, is the extension of tubules into surrounding fat [36]. Tubular carcinoma frequently coexists with other low-nuclear-grade breast lesions, including Columnar Cell Lesions, Flat Epithelial Atypia, Atypical Ductal Hyperplasia, low-grade Ductal Carcinoma In Situ, and Lobular In Situ Neoplasia [34]. These lesions share morphological, immunophenotypic, and molecular characteristics and constitute the low-nuclear-grade neoplasia family.

Tubular carcinoma demonstrates high expression of hormone receptors, luminal cytokeratins, and E-cadherin. It does not express basal cytokeratins, lacks HER2 gene amplification, and is usually negative for epidermal growth factor receptor, p-cadherin, and p53 [31]. Differential diagnoses include benign, small, glandular proliferations of the breast and

invasive carcinomas with a tubular growth pattern. The absence of myoepithelial cells in tubules is the hallmark of tubular carcinoma.

Tubular carcinoma generally has a low incidence of metastases to axillary lymph nodes and low recurrence rates, leading to a favorable prognosis [37].

2. Mucinous Carcinoma

Mucinous carcinoma, also known as mucoid, colloid, or gelatinous carcinoma, consists of malignant epithelial nests floating within extracellular mucin [36]. It accounts for 1–6% of all invasive breast cancers, primarily affecting elderly patients over 60 years of age [38, 39].

Microscopically, tumors are composed of small clusters of uniform epithelial cells with mild nuclear atypia floating in abundant mucus. These cell clusters are arranged in solid, acinar, or micropapillary structures. The mucin, which is almost entirely extracellular, varies in extent and is separated by fibrous septae containing capillaries, as shown in Figure 4 [34].

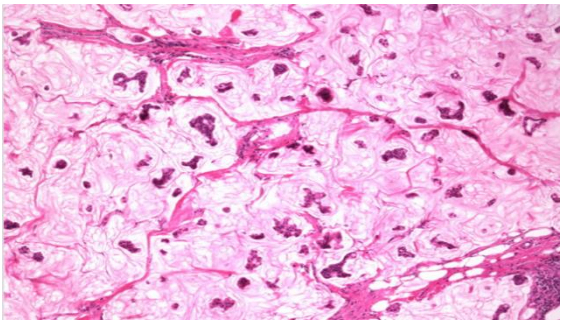

Figure (4): Mucinous carcinoma type A with extracellular mucin and low-grade cellular atypia[34].

Mucinous carcinomas can be subdivided into type A (paucicellular) and type B (highly cellular with less extracellular mucin), with type B tumors typically showing endocrine differentiation [40]. Mucinous carcinoma is generally ER and PR positive and HER2 negative[41].

Pure mucinous carcinoma has a good prognosis, whereas mixed mucinous carcinoma has a worse prognosis.

3. Medullary Carcinoma

Medullary Breast Carcinoma (MBC) is an invasive and malignant subtype of breast cancer comprising 3–6% of all breast cancer cases [42]. It is characterized by young age, large tumor size, and high nuclear grade [43].

MBC is defined by specific histologic characteristics, including complete microscopic circumscription, predominantly syncytial growth patterns, and dense lymphocytic infiltration, as shown in Figure 5 [44].

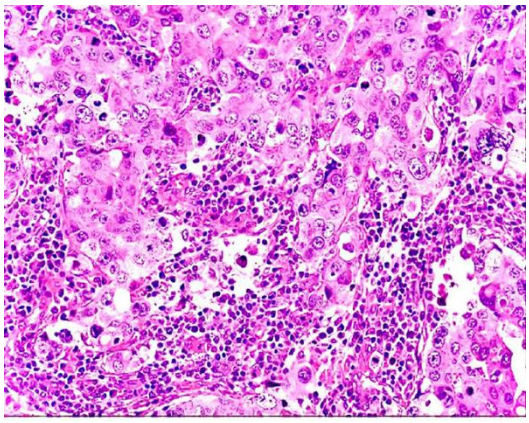

Figure (5): Syncytial growth pattern exhibited by medullary breast carcinoma, with distinct intercellular borders [45].

MBCs frequently exhibit the triple-negative phenotype, with absent ER, PR, and HER2 expression, and are associated with BRCA1 germline mutations and TP53 mutations [46]. Despite aggressive pathological features, MBC has a relatively favorable prognosis compared to IDC [47].

4. Invasive Apocrine Carcinoma (BAC)

Invasive Apocrine Carcinoma (BAC) is a rare type of primary breast cancer. It constitutes approximately 1% of all breast cancers [34].

Apocrine carcinomas usually present as firm, whitish masses with infiltrative borders. Apocrine cells are characterized by abundant eosinophilic or granular cytoplasm, prominent nuclei, and marked nuclear pleomorphism, as shown in Figure 6 [36].

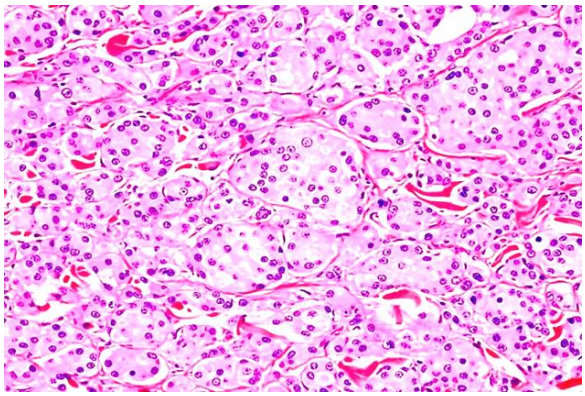

Figure (6): Invasive carcinoma with apocrine features. Anastomosing trabeculae of tumor cells with ample pink cytoplasm and dense nuclei are seen extending through the stroma [36].

Apocrine carcinomas are typically ER and PR negative but androgen receptor (AR) positive in more than 70% of cases.

Differential diagnosis with breast neoplasms with abundant cytoplasm includes granular cell tumor and histiocytoid, lipid-rich, and secretory carcinomas. Breast carcinomas with squamous differentiation or metastatic carcinomas also may have similar features mimicking apocrine breast cancer. Approximately half of apocrine carcinomas have been reported to show c-erbB-2 overexpression and gene amplification, along with losses at 2p and 9q and gains at 2q, 3p, and 13q [48]. Studies evaluating clinical outcomes have contradictory results [49].

5. Invasive Cribriform Carcinoma (ICC)

Invasive Cribriform Carcinoma (ICC) is a rare type of invasive breast cancer, with an incidence of approximately 0.3%-6% in primary breast carcinoma [50]. It may be asymptomatic or present as a small lump, multifocal (10%-20%), or with nodal metastases [51, 52]. Microscopically, it resembles the histological structures of cribriform ductal carcinoma in situ (cribriform DCIS) [53]. All tumor cells are well-differentiated, smaller, more uniform, and have a round or oval nucleus with mild to moderate nuclear atypia. It is divided into pure, classical, and mixed forms [54]. Pure ICC consists of an invasive cribriform pattern in >90% of the lesions. Classical ICC exhibits a predominant invasive cribriform pattern, accompanied by <50% of a tubular carcinoma (TC). If accompanied by 10%-49% of other invasive carcinoma components (except tubular carcinoma), it is classified as a mixed type [50].

ICC expresses luminal cytokeratins and E-cadherin. Pure invasive cribriform carcinoma does not express basal cytokeratins [53]. It should be differentiated from cribriform DCIS, adenoid cystic carcinoma, and other types of breast carcinoma with cribriform areas. ICC is estrogen receptor (ER) and progesterone receptor (PR) positive and lacks HER2 gene amplification and p53 expression [48]. ICC has low metastatic potential and a good prognosis [55].

6. Invasive Papillary Carcinoma (IPC)

Invasive papillary carcinoma is defined by a papillary architecture in more than 90% of the tumor [56]. Tumors without papillary features but associated with encapsulated papillary carcinoma or solid papillary carcinoma should not be classified as IPC [57]. Solid papillary carcinoma with reverse polarity (SPCRP) is a recently described entity, initially referred to as “breast tumor resembling the tall cell variant of papillary thyroid carcinoma” due to its morphologic similarity to thyroid papillary carcinoma. Pure IPC is extremely rare, with limited clinical or epidemiologic data. SPCRP primarily occurs in older women, with a median age of 64 years. Histologically, the tumor cells are columnar to cuboidal, with abundant cytoplasm and

mild nuclear atypia. Nuclei are ovoid, occasionally grooved, and rarely show pseudoinclusions [58].

SPCRP is characterized by solid, circumscribed nodules of columnar epithelial cells, often exhibiting a jigsaw-like growth pattern [59]. The tumors consistently express ER, have a high prevalence of PIK3CA mutations, and relatively low rates of p53 expression. Tumor cells in SPCRP are typically weakly positive for ER and positive for CK5/6, whereas solid papillary carcinoma cells are strongly ER-positive and CK5/6-negative [60]. The differential diagnosis includes metastatic papillary adenocarcinoma from sites like the lung, ovary, or thyroid. SPCRP generally has a favorable prognosis [48, 59].

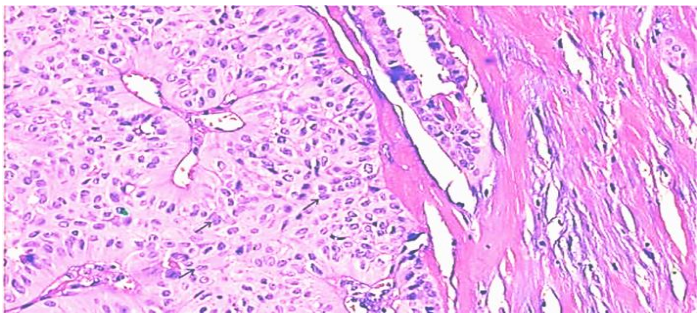

Figure (7): High power view of solid papillary carcinoma with reverse polarity showing tumor cells with low-grade nuclear atypia. Tumor cells have abundant eosinophilic cytoplasms and ovoid nuclei. Some nuclei show nuclear grooves (arrows) [59].

7. Invasive Micropapillary Carcinoma (IMPC)

IMPC is characterized by morular clusters of tumor cells residing within empty spaces [61]. IMPC accounts for 0.9%-1.7% of invasive breast carcinomas in its pure form and up to 7.6% when mixed with other mammary carcinoma types [59]. Patients often present with a palpable mass. IMPC displays an inside-out pattern, where luminal surfaces of epithelial cells face outward into stromal spaces, indicative of reverse polarity [62]. Unlike IPC, micropapillary clusters lack fibrovascular cores [63]. Immunohistochemical staining for epithelial membrane antigen (EMA) and MUC-1 highlights the outer surfaces of tumor cells [48].

IMPC must be distinguished from mucinous carcinoma, which features abundant extracellular mucin absent in IMPC. The majority of IMPC cases are ER and PR positive, with HER2 overexpression observed in 10%-35% of cases [62, 63].

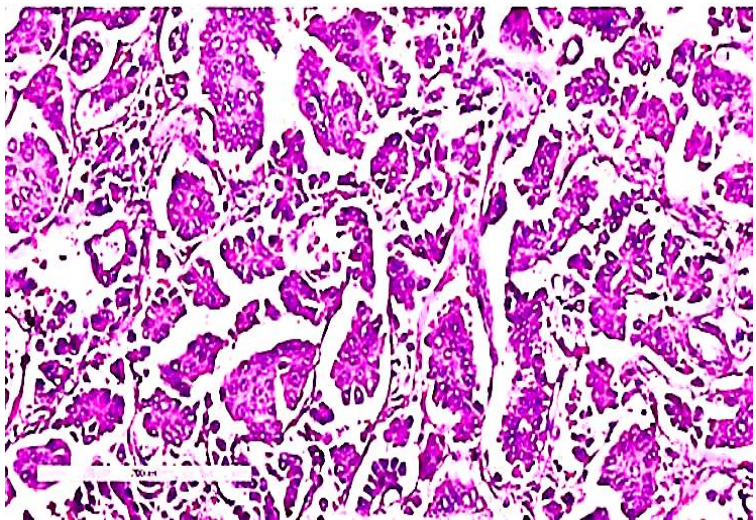

Figure (8): Invasive micropapillary carcinoma. High magnification shows morular nests and micropapillary clusters of tumor cells with vesicular nuclei and discernible nucleoli. Several nests disclose central hollow spaces, while the micropapillary clusters are devoid of central fibrovascular cores. Empty spaces surround the tumor cells [48].

Nuclear Factor-κβ Expression in Invasive Breast Cancer

NF-κβ is a protein complex responsible for DNA transcription regulation, cytokine production, and cell survival. In breast cancer, its abnormal activation is linked to tumorigenesis through enhanced cellular proliferation, angiogenesis, and apoptosis evasion. These processes collectively support tumor growth and metastatic potential. Pathological studies using immunohistochemistry (IHC) have demonstrated a strong nuclear localization of NF-κβ in high-grade breast cancers, indicating active transcriptional roles that promote aggressive behavior[48].

In breast cancer tissues, immunohistochemical (IHC) studies have shown that NF-κβ is primarily localized in the cytoplasm and nucleus of tumor cells. Nuclear localization is particularly significant as it indicates active NF-κβ signaling, which is strongly associated with high tumor grade, extensive lymphovascular invasion, and increased metastatic potential. Findings from IHC analysis provide a direct correlation between NF-κβ activity and advanced pathological features [49].

The NF-κβ signaling pathway operates via two main mechanisms: the classical and alternative pathways. The classical pathway, triggered by cytokines like TNF-α and IL-1β, is highly relevant in breast cancer. IHC studies have shown elevated levels of phosphorylated Iκβ kinase (IKK), a key activator of NF-κβ, particularly in inflammatory breast cancer, underscoring its importance in aggressive tumor biology [50].

NF-κβ plays a pivotal role in promoting epithelial-to-mesenchymal transition (EMT), a key event in cancer metastasis. EMT markers such as reduced E-cadherin and increased vimentin expression are frequently observed alongside elevated NF-κβ activity in IHC-stained tumor sections. These findings suggest that NF-κβ contributes to a loss of cell adhesion and increased invasiveness in breast cancer cells [51].

High levels of NF-κβ activity have been consistently linked to aggressive phenotypes in IBC, including larger tumor size, higher histological grade, and axillary lymph node

involvement. IHC staining frequently reveals intense nuclear NF-κβ expression in triple-negative breast cancer (TNBC), correlating with its poor prognosis and aggressive clinical behavior [52].

NF-κβ's anti-apoptotic effects are mediated through the upregulation of survival proteins such as Bcl-2 and Bcl-xL. IHC analysis often highlights these proteins in NF-κβ positive tumors, correlating with resistance to apoptosis. This finding is particularly significant in understanding therapy resistance in breast cancer, as these survival pathways enable cancer cells to evade programmed cell death [53].

The interaction between NF-κβ and estrogen receptor (ER) pathways has profound implications for hormone receptor-positive breast cancers. Pathological studies have shown that tumors expressing both NF-κβ and ER exhibit altered responses to endocrine therapies such as tamoxifen. This interaction, often detected through dual IHC staining, highlights the complexity of crosstalk between these signaling pathways in breast cancer progression [54].

Elevated NF-κβ activity has been observed in IHC studies of breast cancer tissues, correlating with adverse clinico-pathological features such as lymphovascular invasion, tumor necrosis, and advanced stage. These findings support the use of NF-κβ as a prognostic marker and potential therapeutic target in breast cancer [55].

Therapy resistance in breast cancer is a multifaceted challenge, with NF-κβ playing a central role. By regulating genes involved in drug metabolism and efflux, NF-κβ promotes chemoresistance. IHC staining for multidrug resistance proteins, such as P-glycoprotein, often coincides with high NF-κβ activity, particularly in recurrent and metastatic tumors [56].

The activation of NF-κβ involves upstream kinases like IKK, which phosphorylates the inhibitory protein Iκβα. This phosphorylation marks Iκβα for proteasomal degradation, freeing NF-κβ to translocate to the nucleus. IHC analysis frequently shows elevated expression of phosphorylated IKK in NF-κβ active tumors, providing a molecular basis for its constitutive activation in cancer [57].

Intrinsic and extrinsic factors activate NF-κβ in breast cancer. Intrinsic activation involves genetic mutations in regulators such as IKK, while extrinsic activation arises from cytokine signaling in the tumor microenvironment. Pathologically, IHC studies reveal overexpression of cytokines like TNF-α in the tumor stroma, further supporting the link between inflammation and NF-κβ activation [58].

Tumor hypoxia amplifies NF-κβ activity by interacting with hypoxia-inducible factors (HIFs). IHC staining often shows co-expression of HIF-1α and NF-κβ in hypoxic tumor regions. This interaction promotes angiogenesis and metastasis, contributing to the poor prognosis associated with hypoxic tumors [59].

Targeting NF-κβ therapeutically has shown promise in preclinical models. IHC studies of treated tumors reveal reduced nuclear NF-κβ localization, indicating the efficacy of NF-κβ

inhibitors. However, the challenges of achieving selective inhibition without affecting normal immune function remain significant [60].

Elevated NF-κβ expression in TNBC highlights its role in driving aggressive tumor behavior. Pathologically, these tumors often exhibit high mitotic activity, necrosis, and stromal desmoplasia, all of which are correlated with NF-κβ activation on IHC analysis. This highlights its potential as a therapeutic target in this challenging subtype [61].

NF-κβ profoundly influences the tumor immune microenvironment by regulating chemokines such as CCL2 and CXCL8. IHC studies demonstrate increased infiltration of tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) in NF-κβ positive tumors, suggesting a role in immune evasion and poor response to immunotherapy [62].

Pro-inflammatory cytokines like TNF-α and IL-6 are potent activators of NF-κβ. Pathological analyses frequently reveal elevated levels of these cytokines in the tumor microenvironment, correlating with increased NF-κβ activity and poorer clinical outcomes. This self-sustaining loop underscores the therapeutic potential of targeting this axis [63].

NF-κβ's role in angiogenesis is mediated through its regulation of vascular endothelial growth factor (VEGF). IHC studies show strong VEGF expression in NF-κβ positive tumors, correlating with increased microvessel density. This highlights the importance of NF-κβ in sustaining tumor vasculature and facilitating metastatic dissemination [64].

Hypoxia-induced NF-κβ signaling contributes to radiation resistance in breast cancer. IHC analysis often reveals upregulation of DNA repair proteins and anti-apoptotic markers in hypoxic, NF-κβ positive tumor regions, illustrating its role in therapy resistance and tumor survival under stress [65].

Genetic polymorphisms in NF-κβ related genes influence susceptibility to breast cancer and clinical outcomes. IHC studies provide evidence of differential NF-κβ activity in tumors with distinct genetic backgrounds, suggesting personalized therapeutic strategies based on NF-κβ status [66].

NF-κβ's interaction with the PI3K/Akt pathway creates a survival network within cancer cells. Pathologically, co-expression of activated Akt and nuclear NF-κβ is frequently observed in aggressive tumors. IHC analyses provide strong evidence that these pathways synergize to enhance tumor survival and proliferation, supporting the rationale for targeting both pathways simultaneously [67,68].

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