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Invasive Lobular Carcinoma: A Comprehensive Review

Ms. Diksha Maheshwari[1], Mr. Mukulraj Singh Rao[2], Mr. Adtiya Pant[3], Dr. B. S. Sonigara[4]
[1, 2]*B.Pharm. Students (BNCP)*
[3]*Asst. prof. (Department of Pharmacology, BNCP)*
[4]*Asst. prof. (Department of chemistry, BNCP)*

Abstract: ***ILC is the second most common type of breast cancer, comprising approximately 10% of all cases. Originating in the milk-producing lobules of the breast, ILC is characterized by a unique histological growth pattern driven by the loss of E-cadherin protein.ILC exhibits small, non-cohesive cells that infiltrate the stroma in a single-file pattern and often lacks palpable mass, making it challenging with regard to early detection and treatment. This review provides an in-depth exploration of cause, signs & symptoms, stage, grade, diagnosis, and treatment.***
It also highlights current diagnostic methods, including mammography, ultrasound, MRI, BSGI, and biopsy, and each offers varying degrees of sensitivity due to ILC's unique presentation. Surgery, radiation, chemotherapy, hormone therapy, and targeted therapy are guided by tumor stage and grade. Despite sharing some similarities with IDC. ILC is responsible for its unique biological behavior, difficult diagnostic tasks, and range of responses. ILC patients' diagnostic accuracy and treatment outcomes depend on understanding these nuances.
Keywords: Invasive Lobular Carcinoma (ILC), Breast Cancer, E-cadherin, HER2 Negative,CDH1 mutation, Hormone Receptor Positive(HR+).

I. INTRODUCTION

One kind of breast cancer that starts as a proliferation of cells in the breast's milk-producing glands is called invasive lobular carcinoma. We refer to these glands as lobules.
The term "invasive cancer" refers to cancer that has spread into the breast tissue after breaking out of the lobule where it started. It is possible for the cells to spread to other parts of the body, including the lymph nodes.
About 10% of cases are invasive lobular carcinoma (ILC), the second leading form of breast cancer. Its epidemiology, molecular alterations, and natural history are different from those of the most widespread subtype, invasive ductal carcinoma (IDC). (1,2)
The lack of the cell adhesion protein E-cadherin, which propels the tumor's unusual discohesive growth pattern—in which cells spread throughout the stroma in single file—is one of the unique biological characteristics of ILC. These tumors usually start in the lobules, are more frequently bilateral than invasive ductal carcinoma (IDC), and need a more precise imaging test for diagnosis. They are luminal in molecular subtype and exhibit estrogen and progesterone receptor positivity and HER2 negativity, thus presenting a more unpredictable response to neoadjuvant therapies. (3)
Due to their architecture (alveolar, solid, and trabecular) or cytological features (pleomorphic, apocrine, histiocytoid, and signet ring), several subtypes have been described as "mixed non-classic ILC."(4) Low-grade, estrogen receptor-positive ILC tumors have a good prognosis, but they can spread.(5)

II. CAUSES

ILC emerges from the breast's terminal duct lobular units' epithelial cells. Modifications in the E-cadherin gene, CDH1, cause ILC to lack functional E-cadherin. Although somatic mutations or methylation of CDH1 are present in most ILC tumors, germline mutations in CDH1 cause the clinical condition known as hereditary diffuse gastric cancer and increase the lifetime risk of developing both ILC and diffuse gastric cancer. Less than 10% of ILC tumors are either HR-negative or HER2-positive, with a majority being hormone receptor (HR)-positive and lacking overexpression of human epidermal growth factor-2 (HER2). Although ILC has traditionally been thought of as a homogeneous tumor type, new research shows that it differs from invasive ductal carcinoma (IDC) and that it can be heterogeneous. Few research specifically addresses this tumor type, despite its unique characteristics. Compared to IDC, bilateral breast involvement is more frequent in ILC.

Since the tumor is located in the lobules rather than the ducts and typically does not show up as a mass, it is challenging to find using both conventional imaging methods and physical examination. Because of its unique biological profile, ILC poses special difficulties for the management and systemic therapy of the illness. (3)

III. ENVIRONMENTAL AND LIFESTYLE RISK FACTOR

As the majority of breast cancers are linked to female hormones, any condition that raises exposure to these hormones could be a risk factor. Specifically, reproductive variables such as early menarche, late menopause, poor parity and late age at first birth that are linked to higher exposure to endogenous estrogens produced by the ovaries are known risk factors for breast cancer.(6–9) Also, women who are exposed to exogenous hormones (like those found in MHT or oral contraceptives) are usually at higher risk.(10,11)
Breast cancer is also linked to lifestyle choices. Every 10 g of ethanol used daily is thought to raise risk by 10%. Being overweight or obese is also linked to an increased risk of breast cancer, but only in postmenopausal women. An increase of 5 kg/m² in body mass index (BMI) is connected with an 8% increase in the risk of developing breast cancer. (6)
In contrast, high weight is related to a lower risk in premenopausal women. Again, these relationships can be explained by biological factors: Alcohol use and postmenopausal obesity are associated with increased circulating estrogen levels.While the decrease in female hormone synthesis linked to hormonal cycles in obese women during premenopause certainly explains the inverse connection with breast cancer, greater estrogen levels in postmenopause are most likely caused by extraglandular production in the adipose tissue. (12)

IV. GENETIC RISK FACTOR

According to several studies, germline mutations in the genes CDH1 (which codes for E-cadherin) and BRCA2 are linked to a high chance of developing ILC, while germline mutations in ATM, CHEK2, and PALB2 are linked to a moderate risk. A clinically significant risk of finding ILC is not linked to germline BRCA1 mutations.(13–16) A clinically significant risk of acquiring ILC is not linked to germline BRCA1 mutations. In addition, Yadav et al. found that germline CDH1 mutations, which also lead to diffuse-type gastric cancer, were much more common in patients with ILC, whereas germline BRCA1 and PALB2 mutations were significantly less common. In women with bilateral ILC, germline CDH1 mutations seem to be more prevalent (8%) than in patients with ILC (<1%).(17)
A germline mutation linked to an increased risk of breast cancer was found in 11% of women under 40 in a research of 1434 people having ILC. Furthermore, there is evidence that single nucleotide polymorphisms (SNPs) related with low penetrance breast cancer risk have varying effects on the formation of ILC and NST, with one particular SNP for ILC found on 7q34. (18)

V. SIGNS AND SYMPTOMS

Invasive lobular cancer may initially show no symptoms. Invasive lobular carcinoma may result in the following when it gets bigger:

1) An alteration, such as thickening or dimpling, in the texture or appearance of the skin covering the breast.
2) A newly developed spot of breast enlargement or heaviness.
3) An inverted turned nipple.
4) A section of the breast that has thickened.
5) inflammation of the skin (redness, scaling)
6) Pain in the breast or nipples
7) secretion from the breasts that isn't breast milk.
8) One breast could appear larger than the other. (19–21)

Stages of ILC: invasive lobular carcinoma stages are as follows:(22)

STAGE 1	Stage 1 ILC means that the cancer is small (less than 2 centimeters) and hasn't spread to the lymph nodes or may have spread to only a few nearby lymph nodes.
STAGE 2	Stage 2 ILC means the cancer is larger (between 2 and 5 centimeters) and may or may not have spread into nearby lymph nodes

STAGE 3	Stage 3 ILC means the cancer is large (more than 5 centimeters) and has spread into nearby lymph nodes or lymph nodes near the collarbone.
STAGE 4	Stage 4 ILC (also called metastatic breast cancer) means that the cancer has spread (metastasized) to distant areas or organs of the body. Unlike other types of invasive breast cancer that commonly spread to the bones, liver, lungs, and brain, ILC tends to metastasize to the colon, uterus, ovaries, and stomach.

Here, Stage 1,2,3 are called early stage invasive lobular carcinoma. (23)

VI. GRADE

When invasive lobular carcinoma is diagnosed, it will be given a grade. A cancer grade is a numbering system that describes how abnormal the cancerous cells look under a microscope. Cancer grades are not to be confused with cancer stages; they are separate and different.All breast cancer is graded between 1 and 3. Generally, the lower the grade, the less aggressive the cancer.
Invasive lobular carcinoma grades are as follows:

GRADE 1	The cancerous cells look much like normal breast cells and tend to grow slowly.
GRADE 2	The cancerous cells look much like normal breast cells and tend to grow at a moderate pace (faster than Grade 1).
GRADE 3	The cancerous cells look distinctly different from normal breast cells and tend to grow quickly. Grade 3 ILC presents an increased chance of breast cancer recurrence in the future.(22)

VII.DIAGNOSIS

As ILC usually does not develop a palpable lesion, its unique growth pattern makes clinical diagnosis challenging. Most of the time, this growth pattern is not the same as other invasive breast tumors. This makes it harder to use diagnostic imaging.

1) Mammogram:

Mammogram is an x-ray machine which takes picture of breast from side and from above and helps to detect breast cancer and changes in breast tissue.
Mammograms are only 57% to 81% sensitive at finding ILC. This means that 35% of the time they only show up in one view and 30% of the time they don't show up at all. Because of its unique growth pattern, ILC is challenging to identify using a mammography. ILC may be detected by mammograms showing spiculated opacities, structural deformation, and poorly defined opacities... Mammogram findings of ILC are rare and include calcifications and a well-circumscribed place.(24)

2) Ultrasound:

The breast ultrasound technique helps identify and track the development of breast abnormalities by producing pictures of the breast using ultrasonic waves.
When mammograms have low sensitivity, ultrasound can help detect cancer that may be hidden in dense breast tissue. Therefore, women with thick breasts are the ones who utilize it the most. Because ultrasounds are typically painless and radiation-free, they are safe for both pregnant women and people who are radiation-sensitive. It can be used to track the dimensions and features of breast tumors or tissue irregularities.
The total sensitivity for the identification of ILC has increased from 68% to 88% to 98% during the past few decades due to advancements in ultrasound technology.(25,26) Ultrasound is not usually employed for population breast cancer testing. Despite the fact that it is nearly always used for diagnosis. Some have proposed it as an extra imaging method for women who have thick breasts or who are at a higher risk of developing ILC. (13,27,28)

3) Magnetic resonance imaging (MRI):

MRI is a specialized imaging method that helps identify, diagnose, and track breast cancer by producing a series of detailed images of the breast tissue using a radio wave and a powerful magnet. A computer then assembles the cross-sectional and detailed images of breast tissue created by MRI into a 3D image of the best possible quality. This enables a comprehensive evaluation of breast cancer and gives medical professionals access to structure and abnormalities that may not be visible with other imaging techniques, such as mammograms. Breast MRI, a radiation-free imaging method that helps identify the size of the tumor and whether there are further tumors in the breast or the opposite breast, differs from mammograms in that it does not use x-rays.

The imaging modality that has the highest sensitivity for intraluminal cancer (ILC) is magnetic resonance imaging (MRI), which has a sensitivity ranging from 93% to 100%.(29) The characteristics of high sensitivity include a lack of specificity and an inaccurate estimation of the size of the lesion in twenty percent of patients, the majority of whom have lobular carcinoma in situ. (30,31)

4) Breast-specific Gamma Imaging (BSGI):

Breast-Specific Gamma Imaging (BSGI) is a safe, comfortable imaging technique that can aid in breast cancer diagnosis when a mammogram is inconclusive. This advanced technology is typically used as a non-invasive "next step" when a mammogram shows an area of concern.

BSGI is especially helpful if you have:

- Dense breast tissue
- Areas of concern on a mammogram
- Lumps that can be felt but not seen with mammography or ultrasound
- Breast augmentation that interferes with your mammogram
- Scarring from previous surgeries

Rather than using an anatomical method, breast-specific gamma imaging (BSGI) uses physiologic methods to diagnose breast cancer. A high-resolution gamma camera designed specifically for breast cancer and 99m-technetium sestamibi are used by BSGI to identify breast cancer. BSGI is a way to find breast cancer because of the difference in how radiotracer is taken up by cancer cells compared to normal breast tissue around them. The higher uptake is thought to be caused in part by cancer cells having more blood vessels and mitochondria.(32) Even while previous research looked into using a conventional gamma camera for breast imaging, the inherent size resolution made it impossible to reliably detect nonpalpable and sub centimeter breast tumors. Moreover, photographing the breasts in positions similar to mammography is not possible with a conventional gamma camera, making image correlation more straightforward. Even malignancies smaller than 5 mm can be reliably detected by using a high-resolution gamma camera. BSGI has been shown to be accurate for any change in breast density or the type of cancer that is harmful to the breast. According to our observations, BSGI may enable better detection of invasive lobular cancer as its use grows.(33,34)

5) Breast biopsy:

Any suspicious or abnormal spots discovered in the breast will undergo a breast biopsy followingtests.

A breast biopsy is a medical operation in which a sample of breast tissue is taken out and viewed under a microscope to look for abnormalities or symptoms of breast cancer. In order to obtain the sample, a doctor usually inserts a needle into the breast tissue, which is later examined under a microscope to determine whether any malignant cells are present. Using pictures from an x-ray, ultrasound, or other imaging method, the medical expert directs the needle. The doctor uses the needle to remove tissue from the breast once it has reached the proper location.(35),(23)

VIII. TREATMENT OF INVASIVE LOBULAR CARCINOMA

Breast surgeons, medical oncologists, and radiation oncologists should all be involved in the multidisciplinary treatment of breast cancer. The type of treatment depends on the cancer's anatomic stage, but more and more attention is being paid to the biology of the disease, which can be seen in the tumor's ER/PR/HER2 status, histologic grade, and genomic test results.(23)

1) Breast cancer surgery:

Surgery is often used to treat invasive lobular carcinoma. It is mainly of two types for invasive lobular carcinoma

- Lumpectomy: It is also called breast conserving surgery or partial mastectomy used to treat only early-stage invasive lobular carcinoma when cancer cell is small and not spread.

It is viable treatment option and it removes only cancerous tumor and small amount of healthy margin. impact. Lumpectomy is often followed by radiation therapy which can be effective treatment for early-stage invasive lobular carcinoma with similar outcomes to mastectomy.

The benefit of lumpectomy is that allows the patient to preserve their breast tissue.

- Mastectomy: Mastectomy is the surgical removal of tumor from breast. It is used to treat patients:
  - If the tumor is large
  - If there are multiple areas of cancer within the breast
  - If the patient cannot tolerate or chooses not to undergo radiation therapy after surgery.(23)

2) Radiation therapy:

Radiation therapy is an effective treatment for invasive lobular carcinoma. It uses high energy rays target and destroys cancer cells and prevent them from grow and spread. Radiation therapy is recommended after surgery to eliminate any remaining cancer cell and reduce the risk of local recurrence.

But it can cause

- Breast tissue swelling or firmness
- Skin change (sunburn like rash)
- Fatigue(35),(23)

3) Chemotherapy:

Chemotherapy is a surgical treatment for invasive lobular carcinoma that uses a combination of oral drugs or intravenous drugs to destroy cancer cells or to slow their growth. The use of chemotherapy depends on stage, grade, tumor size, and prognostic factors and features such as hormone receptor and HER2 status. Chemotherapy may be given to the patients before surgery (neoadjuvant therapy) to reduce the tumor size or after surgery (adjuvant therapy) to reduce the chance of cancer returning, or both.(22),(23)

4) Hormone therapy:

Hormone therapy, also called endocrine therapy, uses drugs to block or lower the level of hormones such as estrogen and progesterone in the body, which can help to stop or slow the growth of invasive lobular carcinoma. It may be given to women with hormone receptor-positive (HR+) ILC before and after surgery. Sometimes hormone therapy medicines are combined with targeted therapy medicines. This combination can make hormone therapy more effective. Its side effects include hot flashes, night sweats, and vaginal dryness. More serious side effects include a risk of bone thinning and blood clots .(23)

5) Targeted therapy:

Targeted therapy to treat invasive lobular carcinoma uses drugs that are directed (targeted) at proteins in cancerous cells, most commonly HER2 proteins, slowing down or stopping cell growth. The protein HER2 is the target of the most widely used targeted therapy medications for breast cancer. Extra HER2 is produced by certain breast cancer cells. This protein aids in the growth and survival of cancer cells. Targeted therapy medications do not harm healthy cells; instead, they target the cells that produce excess HER2. It's not likely that treatments that target HER2 will work on invasive lobular carcinomas since most of these cancers don't make any other HER2. Targeted therapy medicines can be used before surgery to shrink a breast cancer and make it easier to remove. Some are used after surgery to lower the risk that the cancer will come back. Other types are only used when the cancer has spread to other body parts.(35),(23)

IX. CONCLUSION

Invasive lobular carcinoma is a slow-growing cancer and often an under-recognized subtype of breast cancer that differs significantly from the more common invasive ductal carcinoma in terms of pathology, biological behavior, and clinical presentation. Due to its diffuse growth pattern, bilateral involvement, and subtle radiological findings, it is harder to diagnose. Imaging advances and better understanding of cause, risk factors, signs and symptoms, stages, and grades improve ILC diagnosis. Despite generally being hormone receptor positive and HER2-negative, ILC responds unpredictably to conventional therapies, underscoring the importance of personalized treatment strategies. More people knowing about this type of breast cancer and using a multidisciplinary approach to treat it can help find it early, make better treatment choices, and give people who have it a better outlook.

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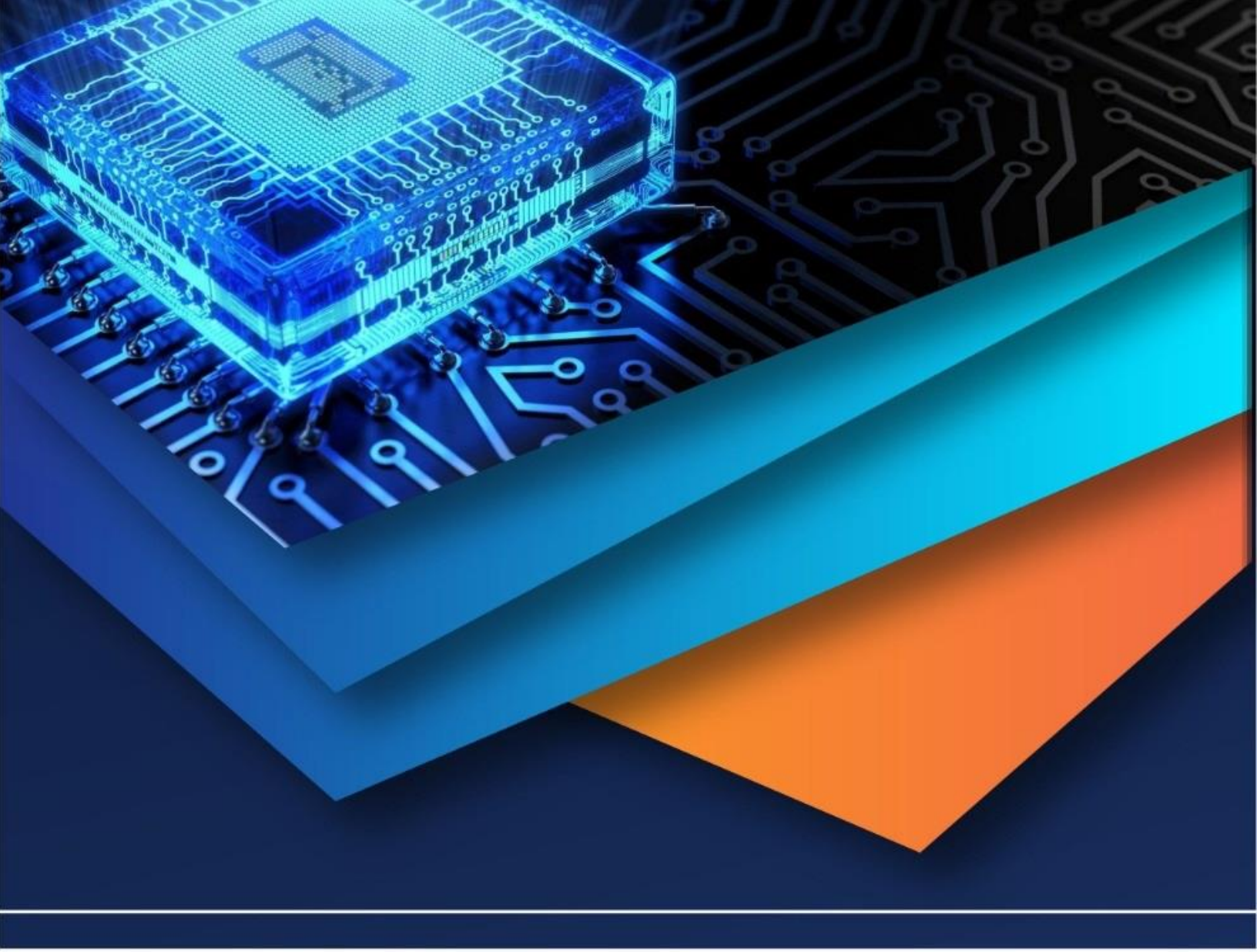

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