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Synchronous bilateral breast cancer with discordant immunohistochemical profiles: A case series and therapeutic implications

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Abstract

Background: Bilateral breast cancer (BBC) with discordant immunohistochemical (IHC) profiles is uncommon but presents significant challenges in diagnosis and treatment. When tumors in each breast exhibit distinct receptor status—such as triple-negative in one and hormone receptor-positive or HER2-positive in the other—treatment decisions become complex.

Methods: We retrospectively analyzed five patients diagnosed between 2020 and 2024 with synchronous bilateral breast cancer exhibiting discordant IHC profiles. Clinicopathological characteristics, treatment regimens, and outcomes were reviewed.

Results: All five patients presented with distinct molecular subtypes between the two breasts. Combinations included triple-negative and luminal A, HER2-positive and luminal B, and other discordant patterns. All were managed with personalized treatment plans addressing each tumor's biology. Treatment included combinations of chemotherapy, endocrine therapy, HER2-targeted therapy, and surgery. All patients completed treatment with no evidence of distant recurrence at the time of last follow-up.

Conclusion: Discordant BBC highlights the importance of individualized treatment strategies and tumor board-based decision-making. Therapeutic planning should be guided by the most aggressive tumor phenotype, while ensuring comprehensive care for both malignancies.

Keywords: Bilateral Breast Cancer; Discordant IHC; Triple-Negative; HER2; Luminal Subtype; Synchronous Tumors; Personalized Therapy.

1. Introduction

Bilateral breast cancer (BBC), defined as the presence of malignant tumors in both breasts either synchronously or metachronously, accounts for approximately 2–5% of all breast cancer diagnoses. Among these, a unique subset of patients presents with discordant immunohistochemical (IHC) profiles, wherein each breast harbors a tumor of distinct molecular subtype—most commonly triple-negative, HER2-positive, or hormone receptor-positive types.

The pathogenesis of such discordance is debated: while some tumors arise as clonally related metastases, many appear to be independent primaries, supported by molecular analyses and histological differences. Clinically, this heterogeneity complicates decisions regarding systemic therapy, surgical approach, and prognosis.

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We present a series of five patients with discordant synchronous bilateral breast cancer managed between 2020 and 2024, emphasizing the therapeutic considerations and literature guiding personalized treatment.

2. Methods

2.1. Study Design and Data Collection

This retrospective case series included five female patients with biopsy-proven synchronous bilateral breast cancer treated at our institution between January 2020 and December 2024. Data were extracted from electronic health records HOSIX, including age at diagnosis, tumor histology, IHC profiles, staging, treatments, and outcomes.

2.2. Diagnostic Evaluation

All patients underwent bilateral breast imaging (mammography and echography supplemented by MRI on a case-by-case basis), core biopsies, and staging workup including axillary assessment and metastatic evaluation (PET-CT or CT scan). Tumors were assessed for ER, PR, HER2, and Ki-67 via immunohistochemistry. HER2 status was confirmed using FISH in equivocal cases.

2.3. Treatment Approach

Therapeutic decisions were individualized and discussed in multidisciplinary tumor boards. Each breast was treated based on its distinct biological profile, incorporating chemotherapy, targeted therapy, endocrine therapy, and surgery as appropriate.

3. Case Reports

3.1. Case 1

A 53-year-old woman presented with bilateral breast tumors. IHC showed TNBC in the left breast and Luminal A (ER+/PR+/HER2−) in the right. She underwent bilateral BCS, received systemic chemotherapy, tamoxifen, and radiotherapy. She remains recurrence-free.

3.2. Case 2

A 48-year-old woman had HER2-positive (ER−/PR−) carcinoma in the left breast and Luminal B (ER+/HER2−) carcinoma in the right. She underwent left BCS and right mastectomy. Adjuvant treatment included taxane-based chemotherapy, trastuzumab, tamoxifen, and radiotherapy. She is disease-free.

3.3. Case 3

A 61-year-old patient had TNBC on the left and HER2-positive disease on the right. She underwent bilateral mastectomy and received anthracycline–taxane chemotherapy, trastuzumab, and radiotherapy. At 18 months follow-up, she is alive with no evidence of disease (NED).

3.4. Case 4

A 56-year-old patient was diagnosed with Luminal B, HER2-positive carcinoma in the left breast and TNBC in the right. She underwent bilateral BCS, followed by HER2-targeted therapy, chemotherapy, an aromatase inhibitor, and radiotherapy. She remains under ongoing follow-up, with no recurrence.

3.5. Case 5

A 44-year-old woman had Luminal A in the left breast and HER2-positive carcinoma in the right. She underwent bilateral mastectomy, received HER2-targeted therapy, an aromatase inhibitor, and radiotherapy. She is disease-free.

4. Results

Table 1 Patient and Tumor Characteristics

Case	Age	Left Breast (IHC)	Right Breast (IHC)	Surgery	Systemic Therapy	RT	Outcome
1	53	TNBC	Luminal A (ER+/PR+/HER2−)	BCS ×2	Chemotherapy + Tamoxifen	Yes	No recurrence
2	48	HER2+ (ER−/PR−)	Luminal B (ER+/HER2−)	BCS on left breast and mastectomy on right breast	Taxane + Trastuzumab + Tamoxifen	Yes	Disease-free
3	61	TNBC	HER2+	Mastectomy ×2	Anthracycline-Taxane + Trastuzumab	Yes	NED at 18 months
4	56	Luminal B HER2+	TNBC	BCS ×2	HER2-targeted therapy + Chemotherapy + AI	Yes	Ongoing follow-up
5	44	Luminal A	HER2+	Mastectomy ×2	HER2-targeted therapy + Arom	yes	Disease free

Abbreviations

- BCS – Breast-conserving surgery;
- ER – Estrogen receptor;
- PR – Progesterone receptor;
- HER2 – Human epidermal growth factor receptor 2;
- TNBC – Triple-negative breast cancer;
- AI – Aromatase inhibitor;
- NED – No evidence of disease;
- IHC – Immunohistochemistry.

5. Discussion

Discordant immunohistochemical (IHC) profiles in bilateral breast cancer (BBC) challenge conventional classification and management algorithms. Although historically considered rare, their detection is increasing due to the widespread use of bilateral imaging and comprehensive pathological assessment [1,2].

5.1. Clonality and Molecular Origins

Studies employing comparative genomic hybridization and next-generation sequencing have shown that many discordant bilateral tumours are genetically distinct, supporting the concept of independent primary tumours rather than metastatic spread. Weigelt et al. demonstrated significant genetic divergence in synchronous tumours [3]. Da Silva et al. found no clonal relationship in approximately 70% of discordant tumours, while Frouws et al. observed differing mutational landscapes in synchronous tumours with discordant profiles [4,5].

These molecular differences often correlate with varying receptor expressions. Luminal A tumours are typically ER+/PR+/HER2− with low proliferation indices, whereas triple-negative breast cancers (TNBC) lack all three receptors and exhibit aggressive biological behaviour [3].

Discordant IHC expression within bilateral disease is of particular importance because it provides insight into the molecular heterogeneity of breast cancer and its independent clonal evolution. This has been supported by reports where synchronous bilateral tumours exhibit distinct transcriptomic and genomic profiles, even when presenting simultaneously [3–5].

5.2. Therapeutic Strategy and Evidence

Clinical guidelines recommend tailoring treatment to each tumour when receptor discordance is present. Key therapeutic strategies include:

- Treating TNBC with systemic chemotherapy irrespective of the contralateral tumour's subtype.
- Administering HER2-targeted therapy when HER2 positivity is detected, even if unilateral.
- Providing endocrine therapy if at least one tumour expresses hormone receptors.

The decision to use chemotherapy may also be influenced by the presence of TNBC or HER2+ disease, even if the contralateral tumour would not typically warrant such treatment. Multigene assays such as Oncotype DX and MammaPrint may help stratify risk in luminal tumours, though their utility in discordant bilateral disease remains under investigation [6,7].

Mamtani et al. emphasized the need for surgical and systemic treatment decisions to reflect the more aggressive tumour subtype [6]. The NCCN 2024 guidelines similarly endorse individualized treatment strategies in the setting of discordant receptor status [7].

In a series of five illustrative cases, the majority of patients underwent breast-conserving surgery (60%) and all received radiotherapy. Systemic therapy was individualized based on receptor status: all TNBC and HER2+ tumours were treated with chemotherapy, HER2-targeted therapy, or both. For hormone receptor-positive tumours, endocrine therapy was included as part of a combined regimen. Notably, two patients had HER2+ tumours in one breast and luminal subtypes in the contralateral breast—requiring dual pathway-directed treatments. In all five cases, outcomes were favourable, with no recurrence or progression reported during follow-up, aligning with prior findings that appropriately treated discordant bilateral disease can achieve excellent outcomes [6,7].

5.3. Prognostic Implications

Discordant bilateral disease does not inherently portend a worse prognosis when managed appropriately. However, heightened vigilance is necessary, particularly in the context of TNBC or HER2+ tumours, which are associated with higher recurrence risk [8,9].

Available evidence and our case series indicate that prognosis is largely influenced by the tumour with more aggressive biological features. This highlights the importance of identifying and prioritizing the higher-risk tumour during treatment planning [9,10].

6. Conclusion

Bilateral breast cancer with discordant IHC profiles necessitates a nuanced and individualized approach to diagnosis and treatment. Multidisciplinary tumour board discussions are essential to evaluate each tumour independently and guide therapeutic decisions. Although evidence remains limited, current data suggest that individualized treatment—guided by the more aggressive tumour—can lead to favourable outcomes

Compliance with ethical standards

Disclosure of Conflict of Interest

The authors declare that they have no conflict of interest.

Statement of Informed Consent

Informed consent was obtained from all individual participants included in the study

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