ISSN 2689-8268 | Volume 6

American Journal of Surgery and Clinical Case Reports

Case Report Open Access

Potential Diagnostic Pitfalls in Lack of Recognition of Histopathologic Changes of Breast Carcinoma Following Neoadjuvant Chemotherapy

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Received: 22 Dec 2022
Accepted: 28 Jan 2023
Published: 06 Feb 2023
J Short Name: AJSCCR

Keywords:

Neoadjuvant therapy; Residual breast cancer; Histopathologic changes

Abbreviations:

H&E: Hematoxylin and Eosin

Citation:

Middleton LP. Potential Diagnostic Pitfalls in Lack of Recognition of Histopathologic Changes of Breast Carcinoma Following Neoadjuvant Chemotherapy. Ame J Surg Clin Case Rep. 2023; 6(5): 1-3

1. Abstract

1.1. Background: The current standard of care for patients with invasive breast cancer is neoadjuvant chemotherapy. The histopathologic changes of residual cancer after such therapy are variable. Few papers illustrate these histopathologic patterns of residual cancer after neoadjuvant therapy. We report the case of residual cancer demonstrating significant cytologic changes from the original tumor.

1.2. Case Presentation: Patient is a 53-year-old female with diagnosis of invasive ductal carcinoma of the left breast and she completed neoadjuvant chemotherapy. Gross examination and intraoperative radiograph show 6 cm tumor bed. Targeted microscopic examination of the tumor bed demonstrates fibrosis, elastosis, and markedly cytologic atypia with high nuclear to cytoplasmic ratio and abundant eosinophilic vacuolated cytoplasm. Ductal carcinoma in situ comprised 90% of the residual carcinoma. Clusters of tumors were surrounded by an intense lymphoplasmacytic response. Sections of multiple axillary lymph node show metastatic carcinoma, consisting of large atypical hyperchromatic cells admixed with an extensive proliferation of foamy histiocytes.

1.3. Conclusion: The management and prognosis of patients with complete pathologic response versus residual cancer are different. Furthermore, recognition of post-treatment residual cancer helps us understand the microenvironment of residual disease and further refine targeted therapy. Therefore, knowledge of variable treatment induced histopathologic features is crucial for diagnosis and further management.

2. Background

Most patients with invasive breast cancer receive neoadjuvant therapy, including chemotherapy, HER-2-targeted therapy, and/or endocrine therapy depending on the tumor type and biomarker profile. These treatments can make inoperable cases operable if the tumor is successfully and sufficiently down staged. As women are increasingly offered chemotherapy to reduce tumor size, evaluation of the treated tumor bed is becoming more commonly performed to evaluate the effectiveness of therapy.

Among patients who do not achieve a pathologic Complete Response (pCR), the histopathologic changes are variable [1]. Excluding the elegantly illustrated cytotoxic effects of chemotherapy by Kennedy et al [1], few papers illustrate the histopathologic patterns of residual cancer after the neoadjuvant therapy.

3. Case Presentation

We present a case of a 53-year-old female diagnosed with invasive moderately differentiated ductal carcinoma of the left breast (ER+, PR+, HER2-) (Figure 1) who completed neoadjuvant chemotherapy with Taxol and Dose-Dense Doxorubicin/Cyclophosphamide

(DDAC). A total mastectomy and left axillary lymph node dissection were subsequently performed. Gross examination revealed diffusely edematous changes, thickened skin, and treated 6 cm tumor bed. The intraoperative radiograph of the sliced mastectomy specimen showed an irregular area measuring 6 x 4 cm (Figure 2) consistent with treated tumor bed.

Microscopic examination of this targeted area demonstrated expansile areas of treatment mediated fibrosis and elastosis with scattered rare clusters of cells exhibiting marked cytologic atypia with increased nuclear to cytoplasmic ratio and abundant eosinophilic vacuolated cytoplasm. Ductal carcinoma in situ (DCIS) with treatment related changes comprised 90% of the residual carcinoma (Figure 3a and b). The neoplastic cells populated atrophic terminal ductal lobular units (TDLUs). Small clusters of tumor cells were surrounded by an intense lymphoplasmacytic response (Figure 3c). Multiple axillary lymph nodes were involved by metastatic carcinoma, consisting of enlarged markedly atypical hyperchromatic cells admixed with a robust proliferation of foamy histiocytes (Figure 3d).

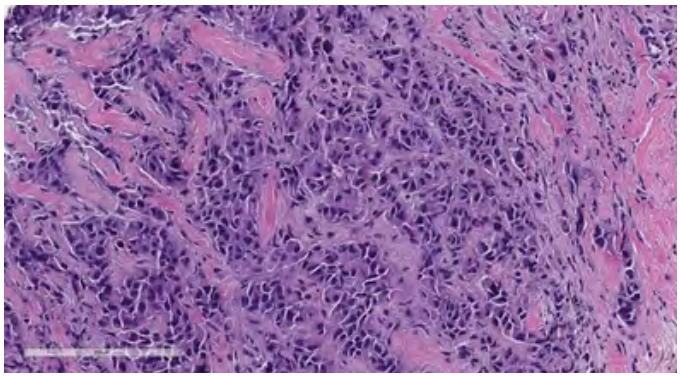

Figure 1: Pretreatment tumor biopsy showing invasive moderately differentiated ductal carcinoma with intermediate grade nuclei H&E X10

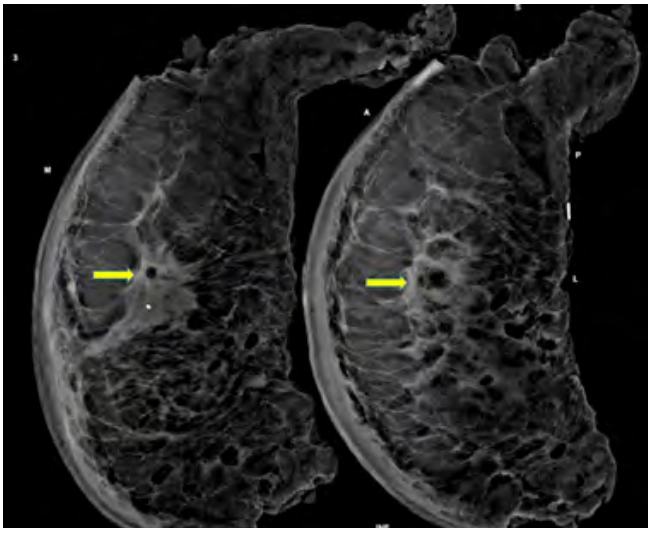

Figure 2: Sliced mastectomy specimen X-ray image post-chemotherapy demonstrates irregular fibrous area in specimen consistent with treated tumor bed (thick yellow arrow). This area is targeted for microscopic evaluation.

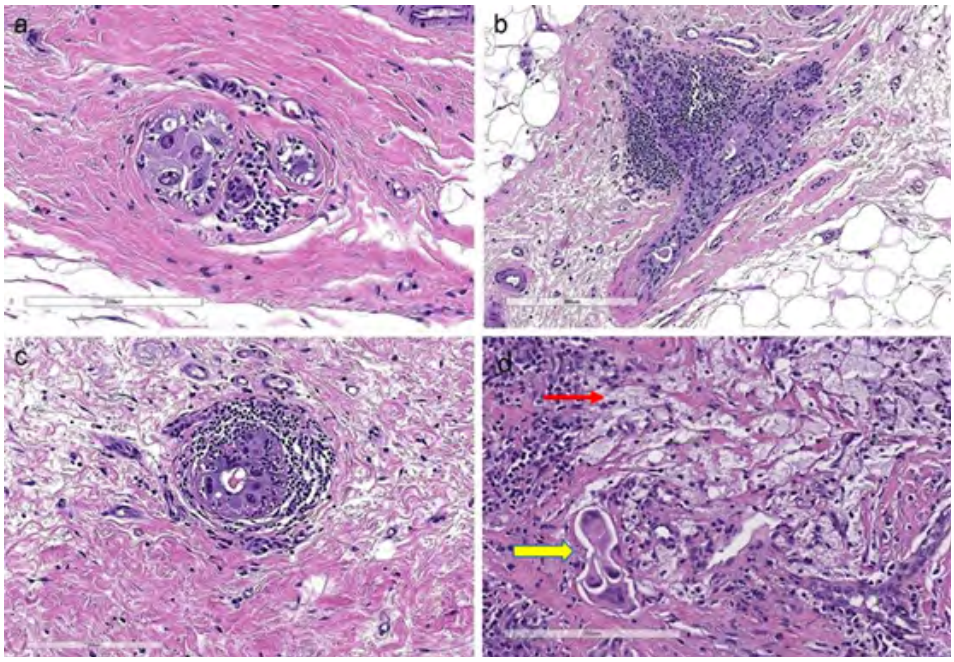

Figure 3: Post treatment histopathologic changes.

Figure 3a shows DCIS with marked nuclear atypia and abundant eosinophilic cytoplasm (H&E x20).

Figure 3b has DCIS with increased stromal TILs (H&E x10).

Figure 3c demonstrates small clusters of tumor cells with stromal TILs (x20).

Figure 3d shows treated residual tumor (thick yellow arrow) within lymph node and adjacent aggregates of histiocytes (thin red arrow) H&E 20X

4. Discussion and Conclusion

Breast carcinoma is known to consist of a heterogeneous population of cells and therapeutic interventions attempt to alter the predominant clonal population, thus inducing histomorphologic changes. Few reports adequately illustrate these changes, which may include marked nuclear atypia, cytoplasmic vacuolization, high number of stromal Tumor-Infiltrating Lymphocytes (TILs) and foamy macrophages, lobular atrophy and characteristic stromal changes, such as fibrosis, myxoid changes, and stromal elastosis [1-4]. Lack of awareness of these histopathologic changes may result in missing residual tumor following chemotherapy and inappropriate down-staging of the patient.

Our case example showed significant cytologic changes from the original tumor, which pre-treatment had intermediate grade nuclear features with hyperchromasia, nuclear molding, notably enlarged nuclei, and abundant eosinophilic cytoplasm. In contrast, post treatment paucicellular residual cancer cells were seen as a single cell or a few clusters of cells, and not infrequently surrounded by lymphoid aggregates, obscuring telltale tumor cells. Importantly, the post-treatment tumor cells in the axilla bared a resemblance to histiocytes which aided in obscuring viable neoplastic cells.

Without knowledge of these variable treatment-induced histopathologic features, the residual cancer could easily be overlooked. The management and prognosis of patients with pathologic complete response versus residual cancer are different. New treatment strategies for residual cancers are being evaluated such as immunotherapy and targeted therapies [5]. Therefore, recognition of residual cancer post-therapy is critical for accurate diagnosis and proper clinical management of patients. Furthermore, evaluation of the persistent histopathologic features will aid in elucidating the microenvironment of residual disease as well as further refine targeted therapy.

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