The interpretation of post-neoadjuvant changes in non-neoplastic breast parenchyma: a case report

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Abstract

Neoadjuvant chemotherapy is the standard of care for many women with early breast cancer, depending on the cancer's hormonal and genomic profile. Post-chemotherapy breast specimens are frequently encountered by the breast pathologist and present an interesting challenge in terms of specimen processing and reporting. We briefly review the literature on current recommendations for processing breast cancer specimens following neoadjuvant chemotherapy and present a case that emphasises the care needed in recognising reactive chemotherapy-related changes in non-neoplastic breast parenchyma to avoid over-diagnosing residual malignancy.

Keywords neoadjuvant chemotherapy; non-neoplastic; reactive changes; treatment effect

Case report

A 52-year old female presented to the breast clinic with a symptomatic mass in her left breast. She was a non-smoker who was otherwise fit and well, with no regular medication. A screening mammogram conducted one month previously was clear. Her menarche was at 14-years old and she was para two. Her first child was born when she was 32-years old and both her children were breastfed for three months. No menopausal symptoms were reported and she had never taken hormonal contraception.

There was a family history of breast and ovarian cancer; one maternal aunt died of breast cancer and another developed ovarian cancer.

Examination confirmed a 17 mm mass in the left upper outer quadrant of the breast. The axilla was clear. Histological examination of the biopsied mass showed an invasive ductal carcinoma; oestrogen receptor positive; progesterone receptor positive; HER-2 negative. The OncotypeDX recurrence score was 51, indicating high-risk and a likeliness to benefit from neoadjuvant chemotherapy.

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Six cycles of TAC (Taxotere, Adriamycin, Cytoxan) were completed prior to left wide local excision and sentinel node biopsy. Post-neoadjuvant radiological investigations demonstrated minimal tumour regression indicating poor treatment response. Histological examination showed a 25 mm grade 3 invasive ductal carcinoma, ypT2 ypN0, with associated ductal carcinoma *in-situ* (DCIS). There was fibrosis and chronic inflammation suggestive of a partial response to neoadjuvant therapy, although greater than 50% of the tumour was remaining. Lobules distant from the main carcinoma showed severe cytological atypia, representing either reactive atypia secondary to treatment effect or further widespread *in-situ* disease. An expert opinion was sought, and the difficulty in distinguishing between *in-situ* carcinoma and reactive atypia was acknowledged but the final opinion was of treatment effect in non-neoplastic acini rather than DCIS.

The patient has subsequently received adjuvant radiotherapy and hormonal treatment but opted against having a mastectomy, given there is no additional survival advantage in this context.

Discussion

Neoadjuvant chemotherapy for early and locally advanced breast cancer is a NICE-recommended treatment choice guided by the cancer's hormonal status and molecular profile.[1] An OncotypeDX regression score was calculated by genomic assessment of 21 genes: 16 cancer-related genes correlated with long-term survival

Methods of improving the accuracy of specimen processing in breast cancer specimens post neoadjuvant chemotherapy

Identification of radiological clips	Sample thoroughly from areas where radiological clips have been identified.
Specimen photography	Orientated photographs including a block key can be a useful reference in both reporting and reviewing cases for MDT.
Specimen radiographs	Radiographs of the sliced specimen can help to identify radiological clips and areas of calcification to be sampled.

Table 1

and 5 reference genes.[2] The regression score indicated high-risk and neoadjuvant chemotherapy was offered to the patient and accepted. The aim of neoadjuvant chemotherapy in this context was to reduce the breast cancer's size, thereby facilitating a more conservative surgical method.

Treatment with neoadjuvant chemotherapy in breast cancer is increasingly common, which presents challenges in specimen processing and reporting. Chemotherapy not only alters the appearance of breast carcinoma but also the associated malignant *in-situ* and non-neoplastic components. Distinguishing between these and determining regression status has important prognostic implications and informs adjuvant management. Despite this, there is no standardised approach to post-chemotherapy specimen processing. A systematic method to processing can help improve reporting accuracy in these difficult specimens (Table 1).[3–5]

Cytological changes apparent in the non-neoplastic breast epithelium post neo-adjuvant chemotherapy

Nucleus	Cytoplasm
Nucleomegaly	Vacuolation
Prominent nucleoli	Granularity
	Clearing
	Eosinophillia

Table 2

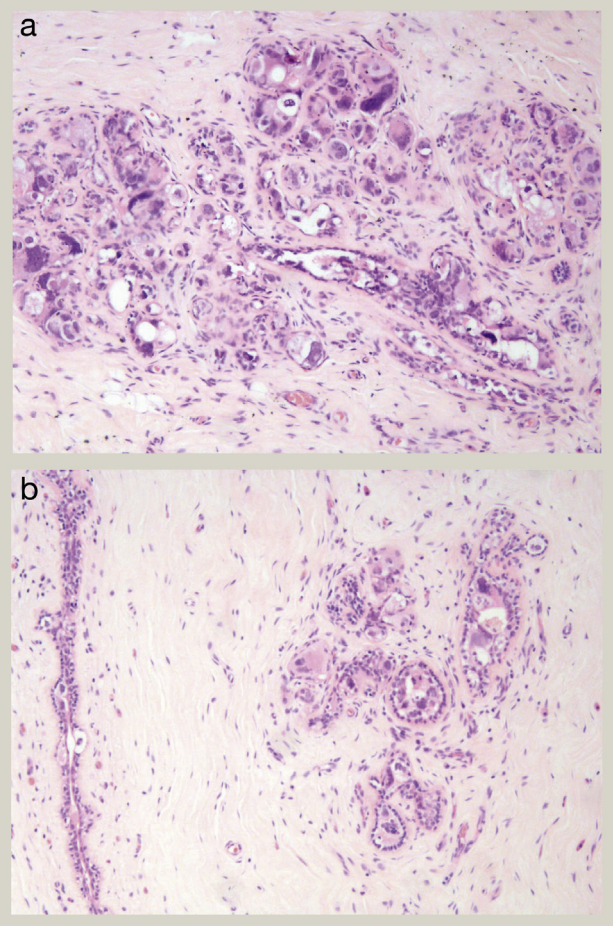

Figure 1 (a) At low power the severe cytological atypia within this breast lobule can be appreciated. At the centre of the image, there is an associated duct which appears relatively preserved. **(b)** In another field of view, lobules with severe reactive epithelial atypia (right) are seen in contrast to the relatively preserved duct (left), where only scattered cells show vacuolation and nucleomegaly.

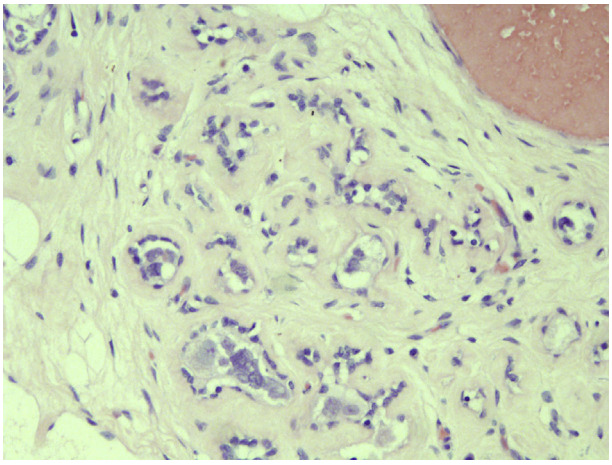

Figure 2 At high-power there is marked thickening of the basement membrane which is a common feature of treatment effect but is also seen in lobular atrophy, which this lobule also shows.

Comprehensive review of the effect of neoadjuvant chemotherapy on breast carcinoma is beyond the scope of this case report; for this we forward the reader to the recent literature and RCPath guidance.[3–5] Here we briefly focus on how neoadjuvant chemotherapy alters the histological appearance of non-neoplastic breast tissue. This is an important distinction for the reporting pathologist to make as chemotherapy causes a range of cytological changes (Table 2).

Reactive atypia secondary to chemotherapy must not be confused with clinically relevant, non-chemotherapy related epithelial atypia. Misinterpretation of reactive epithelial changes at a surgical margin could trigger unnecessary radical surgery. In some classification systems, residual *in-situ* malignancy is not considered to represent complete response to treatment and so a misdiagnosis in this context could lead to overtreatment.[5]

Severe reactive atypia, as seen in this case, is an unusual finding. Care should be taken to compare areas of atypia to residual or pre-treatment carcinoma to confirm that the atypia does not represent further malignancy. The distinction in this case was challenging and required expert consultation; the most important

Practice points

- Specimen radiology, photography, identification of radiological clips and thorough sampling are all methods of improving the accuracy of reporting in the post-neoadjuvant chemotherapy setting.
- Sclerosis and thickened basement membranes are common features of treatment effect in non-neoplastic breast parenchyma secondary to chemotherapy.
- Reactive epithelial atypia can also be seen and can mimic malignancy; care should be taken to compare morphology with any concurrent definite carcinoma or the pre-treatment biopsy.

aspect of the experts' assessment was direct morphological comparison of the reactive lobules and ducts versus the clearly evident DCIS sampled elsewhere (Figure 1).

Marked atrophy of the terminal ductal lobular units occurs more commonly than cellular atypia. This manifests as a reduced number of breast lobules with either global sclerosis or diffuse thickening of lobular basement membranes. This in turn can cause the myoepithelial cell layer to become more prominent. Evidence of cellular proliferation or mitosis should raise the suspicion of malignancy (Figure 2).[4]

Conclusion

Neoadjuvant chemotherapy in breast carcinoma continues to challenge specimen processing and reporting. Reactive epithelial atypia is a less common but well-documented feature of treatment effect. Careful comparison of suspicious areas using the patient's pre-treatment biopsy may help prevent over-diagnosis of malignancy in this context. ◆

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Self-assessment questions

1. What are the most common features of treatment effect in the non-neoplastic breast following neoadjuvant chemotherapy:

A: Sclerosis and thickened basement membranes
B: Severe cytological atypia
C: Mitoses and cellular proliferation

Answer: A – sclerosis is a common feature of neoadjuvant chemotherapy in the non-neoplastic breast. Severe cytological atypia can be seen but it is an unusual feature that should be assessed carefully. Mitoses and cellular proliferation should not be seen and instead may indicate residual malignancy.

2. Which of these is not recommended whilst processing a breast specimen in the post neoadjuvant chemotherapy setting?

A: Specimen photography
B: Identification of clip sites
C: Limiting sampling

Answer: C – specimen photography and identification of clips sites are both recommended practice. The RCPath indicates that sampling should be thorough, especially in the context of therapeutic wide local excisions.