CASE REPORT

Residual mucin and response after neoadjuvant chemotherapy (NAC) in breast cancer

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SUMMARY

Neoadjuvant chemotherapy (NAC) is the standard of care for patients with breast cancer with inoperable disease or smaller tumours who might benefit from a conservative surgery after downstaging of their disease. Nevertheless, evidence shows that preoperative and postoperative chemotherapy are equivalent in terms of long-term survival. Response and histological changes after NAC have been widely studied in invasive ductal carcinoma not otherwise specified, but there is a paucity of characterisation of patterns of response to chemotherapy in less frequent histological types. We report extensive residual mucin deposits after chemotherapy in a woman with locally advanced breast cancer and a prominent mucinous component at diagnosis. Interestingly, residual mucin was co-located with the initial tumour, in the breast as well as in the axillary lymph nodes. The distribution of mucin may be a valuable marker of the extent of mucinous carcinomas prior to NAC.

BACKGROUND

Neoadjuvant chemotherapy (NAC) has become a standard of care for women with stages II and III breast cancer. Response and histological changes after NAC have been widely reported but mostly in invasive ductal carcinoma not otherwise specified (IDC-NOS). These changes include a decrease in cellularity, cell appearance of a higher grade and, more rarely, tumour cell vacuolisation; changes in non-malignant tissue, such as lobular atrophy with hyalinisation and minimal epithelial atypia of lobules and ducts, have also been described.^{1–3} There is, however, a lack of characterisation of chemotherapy response patterns in less frequent histological types.

Breast cancer tumours with a mucin component can be classified as mucinous carcinomas using WHO criteria according to the percentage of that mucinous component.^{4,5} They have a better prognosis and usually present without nodal involvement.^{6,7} There is, therefore, scant literature regarding their pathological response to NAC. We report a case of a patient with locally advanced breast cancer and a prominent mucin component who had a near complete pathological response to chemotherapy with a specific pathological finding of persisting mucin where previously there had been tumour.

CASE PRESENTATION

A 50-year-old woman, perimenopausal, with a previous medical history of coeliac disease but no family history of cancer, in November 2013,

noticed a lump and a feeling of heaviness in her right breast. In the surgical clinic 2 weeks later, clinical examination revealed a large irregular mass occupying almost the entire upper half of the right breast and palpable ipsilateral axillary fixed lymph nodes; in the left breast, there was a smooth mass palpable at the 5 o'clock position.

INVESTIGATIONS

Mammography showed dense glandular breasts with bilateral calcification and prominent abnormal right axillary lymph nodes. Ultrasound of the right breast showed an irregular solid mass containing calcification measuring 57×19 mm at the 9 o'clock position and a large simple cyst in the subareolar region measuring 35 mm, with clinically pathological right axillary lymph nodes; a simple cyst of 16 mm at the 6 o'clock position was identified in the left breast. Core biopsy of the right-sided irregular mass and fine needle biopsy of the nodes both showed IDC, with at least 80% of the material mucinous, grade 3, human epidermal growth factor receptor 2 (HER2) positive (immunohistochemistry (IHC) 3+), estrogen receptor (ER) positive (8/8) but progesterone receptor (PR) negative (0/8).

TREATMENT

The patient's TNM staging was cT3N2Mx with high grade (3) and HER2 positivity as additional risk factors; she was, therefore, a candidate for NAC including an antiHER2 monoclonal antibody prior to surgery. Following discussion with the patient, the agreed plan was for NAC with four cycles of an anthracycline-based regimen followed by four cycles of a taxane plus trastuzumab with mastectomy planned due to the extent of disease at presentation and relatively small breast size. Prior to chemotherapy, baseline breast MRI showed fibrocystic change throughout both breasts, with an extensive area of abnormal enhancement, type 4/5 and 150% enhancement above baseline, measuring at least 50 mm in the right breast laterally, and multiple right axillary nodes each measuring 10×15 mm. The left ventricular ejection was 56% and there was no evidence of distant metastasis on whole body CT scan.

The patient received four cycles of NAC with epirubicin 90 mg/m² (intravenous) plus cyclophosphamide 600 mg/m² (intravenous); after cycle 2, on breast MRI the mass was less apparent morphologically, type 3/5 and 4/5 with 200% enhancement above the baseline. After the fourth cycle, further MRI showed an almost complete radiologic response with only patchy blushes at the site of the known

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Figure 1 Last MRI scan. Enhancement is not seen in the breast, but is seen on the T2 multiseptated cystic area, which would account for the mucin.

tumour (figure 1). The patient then received docetaxel 100 mg/m² plus trastuzumab 6 mg/kg (intravenous) and MRI after two further cycles described a complete radiological response. She completed four cycles of docetaxel plus trastuzumab, followed by a right mastectomy and axillary node clearance in July 2014.

OUTCOME AND FOLLOW-UP

The pathology report described almost complete regression of tumour in the breast, with a 50 mm mucin lake matching the original tumour size, and including a 5 mm focus of residual ductal carcinoma in situ superior to the mucin. Individual scanty tumour cells floating in the mucin, which stained with the cytokeratin marker MNF 116 and were weakly ER positive (2/8), PR negative (0/8) and HER2 positive (3+), were visualised; it was not, however, possible to be certain whether or not they were viable (figure 2). The resection margins were clear with a distance of 1 mm between the mucin and the inferior and posterior margins, and 5 mm for the anterolateral margin. Mucin was also seen in the breast lymphatic nodes and in 4 of the 18 axillary lymph nodes, all of which showed fibrovascular tissue change that was interpreted as a response to chemotherapy. Two possible epithelial cells within the nodal mucin stained with the epithelial marker MNF 116 on IHC; the molecular phenotype of the two nodal cells could not be established. The histological conclusion was of an incomplete response within the tumour and lymph nodes as per the 2012 WHO criteria (8–9). Pathological staging was, therefore, ypTx, ypN0 (i+), ypMx.^{8 9}

Postoperatively, the patient started adjuvant tamoxifen with a view to switching to an aromatase inhibitor after 2 or 3 years; she completed 12 months of trastuzumab and received adjuvant

radiotherapy to the breast and supraclavicular fossa (4 fields to the breast and 2 to the supraclavicular fossa with a total dose in both of 40.05 Gy in 15 fractions over 3 weeks). The patient is alive and without evidence of relapse 2 years from the initial diagnosis.

DISCUSSION

This case report is interesting for two reasons: first, it highlights the classification and characteristics of the mucinous breast cancer subtype; second, there is the finding of extensive residual mucin at the tumour site following NAC.

Mucinous carcinomas

The initial diagnosis of our case report, made on a core biopsy, was of an IDC with mucinous areas consistent with a mucinous carcinoma. Mucinous carcinomas are defined as nests of cells floating in lakes of mucin; by definition, the mucinous component should be $\geq 90\%$ of the tumour for a pure mucinous carcinoma and $>50\%$ but $<90\%$ for a mixed mucinous carcinoma.^{4 5} In our patient, the core biopsy had an 80% mucinous component, consistent with a mixed mucinous carcinoma. The patient's cancer was, however, HER2 positive and grade 3, with nodal involvement, which are uncommon characteristics of both, pure as well as mixed mucinous carcinomas.^{9 10} We found only a single case report of a HER2 positive mucinous carcinoma in the literature,¹¹ and eight HER2 positive cases from a retrospective series of 93 pure mucinous carcinomas in Taiwanese women.¹² Nodal involvement is rare, even with large primary pure or mixed mucinous tumours (WHO).⁴ In a series of 111 cases of mucinous carcinomas (at least 75% of mucinous component), none <1 cm in diameter had nodal involvement, suggesting this could substitute for nodal evaluation, avoiding nodal surgery.⁷ Nevertheless, when mucinous carcinomas do have nodal involvement, this is the single most significant poor prognostic factor.^{13 14} Mixed mucinous carcinomas have a minimally higher rate of HER2 positivity and nodal involvement than pure mucinous carcinomas.¹⁵

On the other hand, mixed mucinous carcinomas have a worse prognosis than the pure subtype but a better prognosis than IDC-NOS.^{15 16} Our patient achieved a near complete pathological response after NAC and trastuzumab, which may reflect the more aggressive phenotype of her cancer.

Pathology of response

Pathological appearances characteristic of responses to chemotherapy in women with mucinous breast carcinomas have been described in a single case report.¹¹ Our case showed an extensive area of residual mucin co-located within the site of the primary tumour, and presumably part of the original tumour, with occasional residual tumour cells the viability of which was

Figure 2 (A) Core biopsy with invasive ductal carcinoma and mucin component ($\times 20$ magnification). (B) Mucinous lakes with scanty tumour cells after neoadjuvant chemotherapy treatment ($\times 10$ CGA).

difficult to characterise, although their molecular phenotype was the same as the primary tumour and they stained for the epithelial marker MNF16. We cannot be confident that the patient had a complete pathological response, but the burden of any remaining disease was certainly very low in the residual primary tumour. Likewise, the four lymph nodes contained mucin with two possible epithelial cells on IHC. Perhaps the unusual histological features, namely, high-grade morphology and HER2 positivity, in a patient with a mucinous carcinoma, may explain the response to the treatment in this case. A similar post-NAC pathological response was described in the earlier case report, with few viable malignant cells within the mucus again suggesting the existence of minimal residual disease. Moreover, they also characterised the presence of two lymph nodes with mucus but without any malignant cells as a response to NAC.¹¹ In both cases, it appears that the mucin present in the lymph nodes represents a marker of prior nodal involvement. The earlier case report did not, however, highlight the extent of the residual mucus after NAC reflecting the extent of the original primary tumour. Finally, the presence of mucin and absence or paucity of viable tumour cells has been reported in patients with rectal cancer and complete pathological response after neoadjuvant chemoradiotherapy treatment; mucin pools did not, however, impact on overall survival.¹⁷

Most carcinomas do not change their morphological appearance after chemotherapy, except for the loss of cellularity and

increase in nuclear atypia.^{1–3} However, changes in pathology subtype have been described in mucinous carcinomas after chemotherapy. In a small prospective series of 40 patients with breast cancer receiving NAC, one patient's pathology changed from a mixed mucinous carcinoma to a ductal carcinoma with metaplastic features, and three patients had ductal invasive carcinoma at diagnosis that appeared mixed mucinous and ductal carcinoma after NAC.¹⁸ Prechemotherapy pathology diagnosis is, however, usually made on a core biopsy that represents a tiny proportion of the whole tumour, so it is difficult to know whether these apparent changes reflect heterogeneity in the original tumour or a response to chemotherapy.

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Patient's perspective

My cancer responded very well to the chemotherapy and, as doctors explained to me, after chemotherapy it had some special appearances that I hope will help them to understand this disease better. As a patient, I found it very interesting to be the subject of an article as opposed to reading research about unknown abstract others. I appreciated being able to read more in-depth information about my condition so giving me a greater understanding.

Learning points

- ▶ Neoadjuvant chemotherapy (NAC) is the standard of care for patients with breast cancer with inoperable disease or smaller tumours who might benefit from a conservative surgery.
- ▶ Pathological response after chemotherapy has been well described for invasive ductal carcinoma not otherwise specified, but there is limited characterisation for less common histological types.
- ▶ This case report offers an insight into pathological response after chemotherapy in breast cancers with a prominent mucin component.
- ▶ Although it would need confirming in a prospective series, the presence of extensive mucin after chemotherapy may be characteristic of a good response to NAC in such tumours, in contrast to the presence of more extensive residual malignant cellular material.
- ▶ Moreover, the extent of mucin deposits may be a valuable marker of the extent of tumour prior to NAC and, therefore, a potential prognostic marker.

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