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Elevated Serum Markers in Non-Invasive Breast Cancer: Five Cases and Review of Literature Introduction

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Abstract

Background: Benign and malignant breast cells can produce measurable serum tumour markers but elevated markers are mostly associated with metastases. When elevated, markers are useful to assess response to breast cancer treatment. We here report on elevated serum tumour markers in 5 cases of non-invasive breast cancer followed by a review of the literature to elucidate this interesting phenomenon. In all cases the tumor markers were determined in anticipation of invasive disease.

Presentation of the cases: In the first case, a solid papillary *in situ* breast carcinoma presents with elevated NSE levels. The second case describes an encapsulated papillary carcinoma with increased levels of CA15.3 and CEA. The 3rd case involves an apocrine ductal carcinoma *in situ* with high CEA levels. The last cases both concern a ductal carcinoma *in situ* associated with increased CA15.3 levels. In all 5 cases we considered different causes of elevated tumour markers and all tumour markers normalized or significantly declined after local therapy only.

Conclusion: We here describe 5 cases of *in situ* breast carcinoma only presenting with increased serum tumour markers. It is discussed to what extend such high levels can be explained by spilling of tumour marker in the surrounding tissue and serum. Further research however is warranted to confirm our hypothesis.

Keywords: Breast; *In-situ* Carcinoma; Serum Tumour Markers

Introduction

Serum Tumor Markers (STM) for breast cancer are molecules that are expressed both by normal as well as cancerous, mostly breast-related, tissue. However, they tend to show a more significant increase in the latter, thereby proportionately displaying the tumor burden. In breast cancer, plasma cancer antigen CA15.3 is the most prominent tumor marker. Carcino-Embryogenic Antigen (CEA) and to a lesser extent, Lactate Dehydrogenase (LDH) and Neuron-Specific Enolase (NSE) are less commonly used tumor markers for breast cancer, but they may provide additional information. A more recently approved useful tumor marker is CA27.29.

However, caution is needed because tumor markers are often non-specific. Numerous benign conditions (inflammation,

endometriosis, sarcoidosis…) too can cause a rise in levels. Therefore, the American Society of Clinical Oncology (ASCO) [1] does not recommend the use of tumor markers neither for breast cancer diagnosis nor for stage evaluation.

Nevertheless, increased levels of STM may be an indicator for advanced disease and the dynamics in levels can be used to assess treatment response. It is unusual to encounter an increased level of STM in association with non-advanced carcinoma of the breast. It is even less common to see elevated tumor markers in cases of *in situ* breast cancer only.

We hereby present 5 cases of non-invasive breast carcinoma associated with elevated levels of tumor markers (NSE, CA15.3 and CEA) and an expected excellent long-term outcome. In all cases, markers were performed because invasive disease was suspected by the respective clinicians.

Case Reports

Case 1

A 59-year-old parous woman presented with a recent onset of unilateral single duct bloodstained left nipple discharge. There were no major events, neither in her personal nor familial history. She never used hormonal replacement therapy (HRT).

Clinically, there was a firm lump behind the left nipple with an extension towards the upper inner breast quadrant of about 7 x 5 cm without signs of mastitis but with obvious skin, nipple and pectoral muscle retraction. The axillary lymph nodes were clinically not involved and the right breast palpated normal, both confirmed on additional preoperative imaging (ultrasound, X-ray, bone scintigraphy), excluding distant metastases.

On ultrasound, the suspicious lesion appeared as a hypo-reflective zone. The Fine Needle Aspiration Cytology (FNAC) of the nipple discharge remained negative. An ultrasound-guided core biopsy of the lump demonstrated a Solid Papillary Ductal Carcinoma (SPC) *in situ*. Preoperative CA 15.3 level was normal (7 kU/L, normal range ≤ 30kU/L) but NSE was slightly elevated (22.3 µg/L, normal range < 16 µg/L).

In spite of its favorable prognosis [2], a mastectomy with sentinel node procedure was performed, as the lesion was too extensive to conserve the breast, cT3N0M0.

Macroscopic examination showed an ill-defined, multi-nodular, white and hard tumor measuring 8.0 x 4.1 x 1.7 cm. Histopathologic mapping confirmed a grade 2 multi-nodular carcinoma *in situ* with solid papillary architecture, neuroendocrine differentiation and the presence of intra- and extracellular mucus. Clear-cut invasion was not observed and the result of the sentinel lymph-node biopsy was negative. The increase in serum NSE-levels subsided postoperatively.

Case 2

A 76-year-old parous lady presented with a clinical palpable lump in the right breast following a trauma. She suffered from a deficient heart valve and developed a Deep Venous Thrombosis (DVT) at age 36 during pregnancy. Her family history was unremarkable. She never used HRT or hormonal contraception. Clinical examination and ultrasound of the breast diagnosed the lump then as a hematoma. However, the breast mass persisted and enlarged.

Clinically we observed right nipple retraction with a sharply delineated retro-areolar palpable lump of 9x10 cm. A mammogram and breast ultrasound this time confirmed the presence of a sharply demarcated mass with reflective material and a papillary growth within a dilated milk duct.

The FNAC was consistent with an in-situ or invasive carcinoma. The laboratory analysis showed highly elevated CA15.3 plasma levels (218 kU/L, normal range < 30 kU/L) and elevated CEA levels (10.1 µg/L, normal range < 3.8 µg/L). Other markers such as CA 19.9, CA125 and NSE were normal.

Preoperative imaging, including chest X-Ray, ultrasound of the upper abdomen, bone scintigraphy and PET/CT scan yielded no evidence for metastases.

The patient was treated by mastectomy and sentinel node biopsy, given the pre-operative diagnosis of a cT3N0M0 tumor of the right breast.

The surgical specimen showed a large haemorrhagic cystic lesion, measuring 7.6 x 7.1 x 3.6 cm. On histology, the lesion was diagnosed as a poorly differentiated encapsulated papillary carcinoma without invasion. The examination of the sentinel node was negative. Postoperatively, the serum CA15.3 and CEA levels restored.

Case 3

This 50-year old, parous lady presented with right-sided nipple discharge. Family history revealed a maternal aunt with breast cancer at age 75. She never used HRT, but was treated with cabergoline for hyperprolactinemia. Imaging of the sellaturcica had never demonstrated a prolactinoma.

On clinical examination, no clear lump was felt, but palpation of the right breast caused abundant milky discharge from one duct. A mammogram indicated a density in the upper half of the breast, measuring about 3 cm with some small clusters of suspicious micro calcifications, which was characterized by meandering ducts on ultrasound. On MRI a pathological contrast capitation of 6.5 x 4.9 x 7.2 cm was noticed in the right upper quadrant. No suspicious axillary lymph nodes were detected and additional imaging (ultrasound, Chest X-ray and bone scintigraphy) noted

no evidence of distant metastases. Biochemical analysis showed a markedly elevated CEA (70.5 µg/L; normal < 3.8 µg/L). CA15.3 levels were normal. Additional determination of calcitonine excluded a medullary thyroid carcinoma.

Cytological examination of the nipple discharge and the FNAC of the lesion showed the presence of poorly differentiated malignant cells. The core needle biopsy of the lesion evinced a grade 3 apocrine DCIS with comedo-necrosis. A mastectomy with sentinel procedure was performed because of the clinical stadium (e.g. cT3N0M0).

The mastectomy specimen confirmed the findings of the needle biopsy. The poorly differentiated DCIS measured about 9 cm in diameter, without evidence for invasion. The estrogen and Progesterone Receptors (PR) were negative, while there was strong CEA expression in the cytoplasm. The sentinel lymph node was negative for malignancy. After the surgery, the CEA levels normalized.

Case 4

A 39-year-old, nulliparous lady, presented with right sided nipple discharge. No relevant antecedents are to be withheld in her personal or family history. An initial mammogram, ultrasound and MRI of the breasts identified benign calcifications in the right breast. A follow-up MRI after 6 months was recommended, this time giving evidence of increased contrast captation of the right sided inner quadrant with a linear pattern. After an additional mammogram to delineate the area, the suspected area was biopsied. Tru-cut biopsy of the zone, complicated by the formation of a hematoma, revealed the presence of a moderately differentiated DCIS with comedo-necrosis. In light of this malignant finding, a CA 15.3 level was determined afterwards, which was elevated up to 92 kU/L. Treatment comprised large excision of the affected zone after 'harpooning'. Definite histopathology findings confirmed the diagnosis of a moderately differentiated DCIS with comedo-necrosis, 4.2 cm in diameter and a DCIS. ER were negative and PR were focally positive. Unfortunately, due to close margins a subsequent mastectomy was deemed necessary. The pathology findings of the mastectomy specimen showed the presence of a solid, cribriform, poorly differentiated DCIS of 5 to 6 cm. Two suspicious lymph nodes were resected, both microscopically negative for metastases. CA 15.3 decreased significantly after local therapy to 35 kU/L.

Case 5

A 67 years old lady mentioned a swelling medial in the right breast since 7 weeks. There was an extensive family history of metastatic breastcancer affecting both the patients' Mother and patients' sister in their 40s. On clinical examination, the tumor was obviously palpable as a 45 mm mass, mobile in relation to thorax and skin.

The mammogram and ultrasound revealed a clear asymmetry in favor of the right breast. The latter showed a hypo-echogenic parenchyma with signs of infiltration, which was a new finding in comparison with previous examinations. An additional MRI of the breasts noted a large zone of 6.3 cm with increased contrast captation. Core biopsies of this zone diagnosed the lesion as a moderately to poorly differentiated DCIS. CA 15.3 level determination after biopsy taking was 61.9 kU/L. A mastectomy with sentinel node procedure was felt to be the treatment of choice. The definite pathology report of the mastectomy confirmed the presence of a 8 cm poorly differentiated DCIS in the inner upper and lower quadrant. ER were positive (7) and PR negative. All 3 sentinel nodes yielded no metastases. CA 15.3 level after the surgery showed normal values.

Discussion

In breast cancer, mainly plasma cancer antigen 15.3 [3] (CA15.3, MUC1) and Carcino-Embryogenic Antigen [4] (CEA) to a lesser extent are the most widely defined serum tumor markers at diagnosis, during surveillance and to assess treatment response.

CA 15.3/MUC1 [5,6] is a transmembrane glycoprotein found in normal tissue. It tends to be overexpressed in cancerous tissue and plays an important role in tumor development and metastasizing as this glycoprotein can interact with - and thereby promote - aggregation, adhesion, migration and invasion. In the process of tumor progression, the basement membrane, framing the tumor, is interrupted and Circulating Tumor Cells (CTCs) are released in the surroundings and in the bloodstream. Due to the abundant presence of MUC1/CA15.3 on the surface of the CTCs, CA15.3 is frequently increased in case of metastatic breast cancer; hence the widespread use of this antigen in detecting CTCs [5].

We need to be aware of falsely elevated serum tumor markers; after administration of granulocyte colony-stimulating growth factors (G-CSF) [7], in the direct postoperative period and as an initial response to systemic treatment like chemo- and endocrine therapy [8]. Elevated levels of CA 15.3 can also be found in numerous other conditions; benign (breast, liver, lungs as well as sarcoidosis, hypothyroidism) as well as malignant (lung, ovarian, endometrial, gastrointestinal and bladder)[8] and rarely in healthy individuals.

Lactate Dehydrogenase (LDH) and Neuron-Specific Enolase (NSE) can give additional information, but these serum markers are less commonly used in the setting of breast cancer. The highly hypoxic environment in tumour cells activates the anaerobic metabolism. Determination of LDH (especially LDH-A), is therefore a good method to detect haemolysis. NSE can be identified in neuronal and neuro-endocrine tissue (normal range <16,3µg/l) and an increased NSE level can be encountered in the presence of a solid papillary carcinoma.

A more recently added and very promising tumormarker is CA27.29. Similar to CA15.3 it concerns a MUC 1 glycoprotein [9].

In all cases described above, the tumor markers were determined in anticipation of invasive disease. The remarkable fact was the significant rise in circulating NSE, CA 15.3 and CEA levels respectively, in the absence of an invasive lesion and despite a negative search for concomitant causes. The tumor markers normalized or decreased significantly post local therapy, providing additional support of their origin.

Similarly, Ichihara and Aoyama (1994) reported a patient with a DCIS and an increased level of CA15.3 [10]. They explained that the secretory activity of the tumor cells resulted in dilated ducts and cysts. A subsequent disruption of the cyst with extravasation of the secretion in the surrounding connective tissue stroma could originate the elevation in tumor markers. Rosen [11] debated that an incidental trauma or even random daily activity coud be the underlying mechanism of cyst-rupture.

This phenomenon can elucidate our findings. Our first case reports a solid papillary carcinoma featured by irregular borders and intra- and extracellular mucinous secretion. Extravasation of mucin may be responsible for the increase in NSE. Our second patient initially presented herself on the occasion of a trauma. This trauma may have provoked disruption of the tumor with spilling of its content, including CA 15.3, facilitated by the lack of a continuous layer of myoepithelial cells surrounding the tumor.

Whether or not the expansile character of papillary lesions with pushing borders makes them prone for rupture, it needs to be further explored. Thirdly, we describe an apocrine DCIS with strong expression of CEA in the cytoplasm as well as in serum. Apocrine DCIS are characterized by abundant eosinophylic and granular cytoplasm and are found to distend and distort ducts and lobular units [12]. Rupture (spontaneous or traumatic) of the cyst could have induced the effluence of cytoplasm and CEA. Comparable with the theory behind the second case, it is very likely that trauma caused by the biopsy is responsible for the increase in CA 15.3 as described in the fourth and last case.

We believe the relevance of this article is dual. Firstly, in the setting of breast carcinoma, elevated tumor markers are often assumed to be associated with metastatic disease. Different approaches account for metastatic carcinoma. When one is not aware and does not acknowledge that the rise in tumor markers might potentially be harmless, it can lead to over- and possibly unnecessary treatment as neo- or adjuvant chemotherapy. Secondly, it is important to incorporate this information when counseling patients. Taking into account that an increased level could be a consequence of a subclinical metastasis, it is recommended to reassess the tumor markers postoperatively as a persistent elevated marker might prompt different follow-up. Furthermore, in the case of elevated tumor markers without obvious metastasis, other investigations could be considered, for instance whole-body diffusion magnetic resonance imaging.

The true incidence and impact of this occurrence is yet unknown and likely underestimated. Therefore, we would like to raise awareness and encourage further research which should focus on the microscopic search for ruptured tumor cells with leakage of their substance in the immediate surroundings. This could help to identify more cases and map the clinical importance.

Conclusion

We herein report five cases of non-metastasized breast carcinoma, all outstanding by an unexpected accompanying elevation of serum tumor markers. None of the five case studies showed evidence of invasion, nor metastasis, supported by the fact that tumor markers decreased significantly or restored completely after local therapy only. A possible explanation of this peculiar phenomenon could be rupture of the tumor - caused by trauma as well as random daily activity - with subsequent spilling of the content (secretion, epithelial cells, tumor antigen) and pervasion of the surrounding stroma, leading to an innocent increase in serum tumor markers. As this trauma could also be caused by obtaining biopsies, as demonstrated in the last 2 cases, caution is needed when interpreting the serum tumor markers levels after invasive diagnostic procedures have taken place.

Clinical practice points

- Tumour markers associated with breast carcinoma can be elevated in the absence of metastatic disease.
- Rupture of the breast-tumour can cause an increase in serum tumour markers.

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