Rare disease

Adenoid cystic carcinoma of the breast with cerebral metastatisation: a clinical novelty

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Correspondence to Dr Ines Silva, inespiresilva@gmail.com**Summary**

Adenoid cystic carcinoma (ACC) is a rare variant of adenocarcinoma of the breast. It affects mainly minor and major salivary glands, but may also occur in many others locations such as: breast (<1% of all breast cancers), lung, trachea, cervix and Bartholin's gland. Its prognosis is excellent, contrary to the extra-mammary form. In fact, metastatisation is rare (there are only seven clinical cases with metastatisation described in literature and the lung is the most affected organ) and when it occurs, generally, there is no axillary node involvement. The authors present the case of a 37-year-old patient, Caucasian, premenopausal, referred to our Cancer Institute with the diagnosis of ACC of the right breast. This case was peculiar because of its multiple and fatal metastatisation pattern—nodal, pulmonary, hepatic, osseous and late multifocal cerebral involvement (brain stem and cerebellum). This is the first case-report of ACC with cerebral metastatisation.

BACKGROUND

Adenoid cystic carcinoma (ACC) of the breast is an infrequent form of breast cancer. The clinical case presented underlines a completely different form of presentation and pattern of evolution comparing with typical ACC. In fact, our patient had a multiple metastatisation pattern—nodal, pulmonary, hepatic, osseous and later on, with multifocal cerebral involvement (brain stem and cerebellum) that was fatal. This is the first case-report described in the literature with cerebral metastatisation.

CASE PRESENTATION

A 37-year-old, Caucasian female patient was referred to our Cancer Institute in July 2004 with the diagnosis of ACC of the breast. No other disease was known. Of note, in her gynaecological history was: menarche at age 14, regular menses, no use of oral contraceptives and had never been pregnant. She had a heavy family history: maternal grandfather died with prostate cancer and maternal grandmother with gastric cancer.

In the beginning of the year of 2004, she presented a lump located in the upper outer quadrant of the right breast related with homolateral palpable axillary nodes. At this time, a biopsy performed in her local hospital suggested the possibility of ACC. Later on, radical mastectomy was performed and confirmed this histological diagnosis. The tumour consisted of a solid variant, with 3 cm; negative estrogen receptor (ER), progesterone receptor (PR) and C-erb2; 3/25 positive nodes (T2N1Mx). In order to have a specialised oncological care she was transferred to our Cancer Institute in July of the same year.

Frozen-sections were reviewed and confirmed this diagnosis: solid variant of ACC with basaloid characteristics (described by Chin and Rosen in 2002); poorly differentiated G3 (Elston and Ellis classification); infiltrative limits; and with vascular invasion (figure 1).

TREATMENT

She started the treatment with chemotherapy (six cycles of adriamycin and cyclophosphamide) and radiotherapy. She became asymptomatic until 2006 when pulmonary and hepatic metastatisation appeared (figure 2). At this time, a new chemotherapy scheme was performed with docetaxel e vinorelbin (six cycles).

OUTCOME AND FOLLOW-UP

The disease stayed stable till 2007 when stem cerebral, cerebellar (figure 3) and bone metastatisation were noted. In this occasion, a paliative chemotherapy with perfusion of 5-fluorouracil was tried. The patient died in February 2007.

DISCUSSION

The ACC of the breast is a rare subtype of cancer (corresponding to <1% of all breast cancers)^{1–5} that occurs mainly in women between the age of 50–60.¹ Only 150 cases have been reported in the literature to date⁶ (five cases of men), generally as case-reports or small case series (with less than 20 patients) from the reference cancer centres.⁶

ACC has an excellent prognosis, contrary to the extra-mammary form (5-year survival is almost 90% for the former and only 30%–50% in the latter).⁶ Moreover, in ACC of the breast, the metastatisation is rare (there are only seven clinical cases with metastatisation described in the literature, and the lung is the most affected organ) and when it occurs, generally, there is no axillary node involvement,^{1 3 6–10} contrary to the extra-mammary form where 1/3 of patients present regional and distant metastatisation at the time of treatment.

The cell of origin of ACC remains controversial. The ductal epithelial cell or the myoepithelial cells alternatively have been considered as its source. However, today's belief is that it derives from a cell which can produce every epithelial elements of the gland (ductal and acinar).⁹

Figure 1 Breast lump biopsy disclosing a solid variant of adenoid cystic carcinoma (HE-amplification 40x).

Figure 2 Multiple metastatisation pattern: hepatic metastasis in abdominal CT.

ACC has a peculiar histology, constituted mainly by small basaloid tumour cells growing in a tubular, cribriform or solid pattern. According to the predominant growth pattern, ACC are divided in three histological variants: cribriform, tubular or solid.^{1 5} The solid variant is the most

aggressive.^{1 3 6 9} ACC is a tumour with a predilection for perineural infiltration; moreover, it also presents myoepithelial contractility, that leads to tenderness.⁷

Biochemical studies showed that these tumours are characterised by: having low nuclear grade, being negative

Figure 3 Multiple metastatisation pattern: cerebral and cerebellar metastasis in head CT.

for estrogen and PR, and being DNA diploid. Moreover, the majority of those tumours have low proliferative activity and absence of p53 protein expression.¹⁰

The most frequent presenting symptom of ACC of the breast is a well-demarcated, movable mass which may be tender to palpation if there is growth in the perineural spaces.¹⁻⁶ However, fixation to the overlying skin, nipple retraction or invasion of the pectoral muscle are uncommon.⁶

All quadrants seem to be affected, with a particular trend for the peri-areolar region. The most striking feature of ACC of the breast, which is in stark contrast with ACC of salivary glands, is the excellent long-term prognosis: a 90%–100% 10-year survival rate is reported, and lymph node metastases are rare, as well as distant metastases, which affect mainly visceral organs. It is usually small with a mean diameter of 2 to 3 cm. Bilateral ACC are rare.¹⁻⁶

The typical mammographic features of this type of tumour are a circumscribed, lobulated nodule. However, there is no relationship between the mammographic feature and the histological pattern.¹

The differential diagnosis of ACC includes: cribriform intraductal carcinoma, invasive ductal carcinoma with a cribriform pattern, papillary carcinoma and mucinous carcinoma.⁹

The immunohistochemical studies show intense positivity for S-100 protein and actin (indicating myoepithelium differentiation) and the inner cell layer expressed keratin (indicating ductal epithelium differentiation) in those patients, confirming the diagnosis of ACC.⁹ The defining molecular feature of ACC of the salivary glands and breast appears to be the presence of a recurrent chromosomal translocation t(6;9)(q22e23;p23e24), which generates a fusion transcript involving the genes MYB and NFIB.⁹ Unfortunately, this molecular feature was not investigated in our patient.

ACCs of the breast also show a basal-like phenotype. The majority of basal-like breast cancers lack or show low levels of ER and PR, lack HER2 protein overexpression and HER2 gene amplification, whereas they express genes and proteins usually found in 'basal'/myoepithelial

cells of the normal breast including high-molecular-weight cytokeratins (5/6, 14 and 17), P-cadherin, caveolins 1 and 2, nestin, α B crystallin, CD109 and epidermal growth factor receptor (EGFR) and in a minority of cases, harbour EGFR gene amplification or aneusomy. They are significantly more aggressive than tumours of other molecular subtypes. However, breast-ACC is characterised by rare regional lymph node involvement, a favourable prognosis with excellent survival, and absence of associated cancers. These findings reinforce the importance of tailored treatments for breast-ACC and lend credence to the apparent heterogeneity of basal-like breast cancers.

Since ACC is a rare neoplasm, it would be impossible to compare the treatment modalities prospectively. From a retrospective review, certain observations can be made: 1) there is much less prognostic significance of negative axillary lymph node metastasis in these patients; 2) it has been suggested that the system used for ACC of the salivary glands is prognostic and should be used to guide treatment options. Unfortunately, this observation is based on a small number of cases and its accuracy cannot be fully evaluated.⁴

Initially, wide local excision was suggested as being curative because of the prolonged clinical course, good prognosis and almost non-existent lymph node involvement. However, due to the documented recurrence of the tumour after local excision, most authors would recommend simple mastectomy unless the lesions are large or there are clinically enlarged axillary lymph nodes.¹⁻⁶

Radiotherapy has rarely been used to treat adenoid cystic carcinoma of the breast, but has been successfully used to treat adenoid cystic tumours of the head and neck. As clinicians gain experience with breast-preserving surgery and radiotherapy for treating breast tumours, these methods may prove to be as effective as simple mastectomy for treating affected patients.⁸⁻⁹

Close follow-up (annual chest x-ray and a thorough physical examination) after a simple mastectomy is still necessary despite the excellent prognosis of this disease since local recurrence and distant metastasis occur, although rarely and generally long after the initial event.¹⁰

Learning points

- ▶ ACC of the breast is a rare subtype of cancer (corresponding to <1% of all breast cancers).
- ▶ ACC has usually an excellent prognosis, contrary to the extra-mammary form.
- ▶ ACC has a peculiar histology, constituted mainly by small basaloid tumour cells growing in a tubular, cribriform or solid pattern.
- ▶ Multiple site metastatisation has seldom been described, with no prior reports of cerebral metastatisation.

Competing interests None.

Patient consent Obtained.

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