Small cell neuroendocrine carcinoma of the breast: a report of three cases and review of the literature

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Small cell neuroendocrine carcinoma (SCNC) has been described in many extrapulmonary sites including breast, larynx, gastrointestinal tract, prostate, bladder, ovary, and cervix. The histological appearances of these tumours in all sites are similar. Reports also suggest that the clinical course of extrapulmonary SCNC is as aggressive as its pulmonary counterpart. Primary SCNC of the breast is as rare as it is in other extrapulmonary sites. Fewer than 30 cases have been reported in the literature, with the largest series of nine cases reported by Shin et al. This tumour is thought to be distinct from tumours of the usual type with neuroendocrine differentiation. The distinction is particularly important in view of the perceived more aggressive behaviour of SCNC. We report three cases of primary SCNC of the breast on our file, one of which has been reported previously.

CASE REPORT

Case 1

A 46 year old, para 0, woman presented with a right breast lump. Clinical examination revealed a painless, firm mobile mass with no palpable axillary lymph nodes. She had no relevant past medical history. Her father had carcinoma of the thyroid gland but there was no family history of breast cancer. Clinical and radiological investigations (computed tomography and positron electron tomography) did not reveal tumour elsewhere in the body. The patient had simple mastectomy of the right breast of short duration. She was a smoker and known asthmatic. She had ovarian cystectomy 30 years before the breast lump, the histological diagnosis of which is not known. There was no relevant family history. Clinical examination revealed a firm subareolar mass with no axillary lymphadenopathy. Radiological and clinical examination failed to reveal tumour elsewhere in the body. She had a simple lumpectomy, which was diagnosed as SCNC with foci of an in situ ductal component. The size of the tumour was 1.7 cm. Axillary clearance was not performed. She then had radiotherapy and six courses of cisplatin and VP16. The patient died of disease 20 months after surgery.

Case 2

A 60 year old woman presented with a subareolar mass in her right breast of short duration. She was a smoker and known asthmatic. She had ovarian cystectomy 30 years before the breast lump, the histological diagnosis of which is not known. There was no relevant family history. Clinical examination revealed a firm subareolar mass with no axillary lymphadenopathy. Radiological and clinical examination

Table 1 Immunohistochemical procedure and antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Dilution</th>
<th>Pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAM5.2</td>
<td>Becton Dickinson, Oxford, UK</td>
<td>Neat</td>
<td>None</td>
</tr>
<tr>
<td>CK7</td>
<td>BioGenex, San Ramon, California, USA</td>
<td>1/50</td>
<td>Protease</td>
</tr>
<tr>
<td>CK20</td>
<td>Dako, Glostrup, Denmark</td>
<td>1/100</td>
<td>Protease</td>
</tr>
<tr>
<td>NSE</td>
<td>Dako</td>
<td>1/200</td>
<td>Pressure cooker</td>
</tr>
<tr>
<td>PGP9.5</td>
<td>Dako</td>
<td>1/100</td>
<td>Pressure cooker</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Dako</td>
<td>1/100</td>
<td>None</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>BioGenex</td>
<td>1/50</td>
<td>None</td>
</tr>
<tr>
<td>ER/PR</td>
<td>Dako</td>
<td>1/50</td>
<td>Pressure cooker</td>
</tr>
<tr>
<td>HER2</td>
<td>Dako</td>
<td>Neat</td>
<td>Boil to 97°C</td>
</tr>
</tbody>
</table>

CK, cytokeratin; ER, oestrogen receptor; NSE, neurone specific enolase; PR, progesterone receptor.

Abbreviations: CK, cytokeratin; SCNC, small cell neuroendocrine carcinoma; WHO, World Health Organisation
(neurone specific enolase, PGP 9.5, chromogranin, and synaptophysin). The clinical charts were also reviewed.

**CLINICAL FINDINGS**

All the patients were female, and their ages, clinical findings, treatments, and outcomes are outlined in Table 2. None of the patients had a history of previous carcinoma or family history of breast cancer. One patient was a smoker. They all presented within one to two months of noticing the tumour. All the patients had lumpectomy followed by irradiation to the chest wall and regional lymph nodes, in addition to six courses of chemotherapy (cisplatin and VP16).

**PATHOLOGY FINDINGS**

**Gross**
The tumours were 1.0 cm, 1.7 cm, and 1.7 cm, respectively, with poorly circumscribed fleshy white to tan cut surfaces and focal areas of necrosis. The 4.0 cm axillary lymph node in the third patient was completely replaced by tumour.

**Microscopy**
All three tumours had similar morphology. They were composed of fairly uniform small dark cells disposed in nests and trabecular patterns separated by bands of fibrous tissue. The cells had a high nucleocytoplasmic ratio, small hyperchromatic nuclei with inconspicuous nucleoli, scanty cytoplasm, and poorly defined cytoplasmic borders. There were areas of dirty necrosis and the mitotic count ranged from 10 to 20/10 high power fields. Foci of an in situ component in the infiltrating tumour were identified in case 2 (Fig 1). No in situ or invasive ductal or lobular carcinoma of the usual type was seen.

**Immunohistochemistry**
Table 3 shows the results of immunoperoxidase staining. The tumours were negative for CD45 and HMB45. The in situ components in case 2 showed a similar immunohistochemical profile to the invasive component.

**DISCUSSION**

Primary SCNC of the breast is a rare tumour with less than 30 cases reported in the literature. Most cases are found in women, as is the case with breast carcinoma of the usual type. Only one case occurring in a 52 year old man has been reported in the literature. The reported age of incidence varies from 40 to 70 years, with a higher incidence in women greater than 60 years. There is considerable similarity between the morphological and histochemical features of these tumours and pulmonary small cell carcinomas.

The histogenesis is still unclear, because the presence of neuroendocrine cells in normal breast has not been proved conclusively. It has been suggested that SCNC is a variant of metaplastic carcinoma arising from usual lobular or ductal carcinoma. This position is strengthened by the dimorphic appearance of the tumour in a large number of reported components in case 2 showed a similar immunohistochemical profile to the invasive component.

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**Table 2 Clinical summary of the cases**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Node</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>Right</td>
<td>1.0</td>
<td>Clinically negative</td>
<td>Lumpectomy, irradiation, and chemotherapy</td>
<td>Free of disease (48 months)</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>Right</td>
<td>1.7</td>
<td>Clinically negative</td>
<td>Lumpectomy, irradiation, and chemotherapy</td>
<td>Dead within 20 months</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>Left</td>
<td>1.7</td>
<td>Positive ipsilateral node</td>
<td>Lumpectomy, irradiation, and chemotherapy</td>
<td>Alive with disease (6 months)</td>
</tr>
</tbody>
</table>

**Table 3 Immunohistochemical pattern of the tumours**

<table>
<thead>
<tr>
<th>Case</th>
<th>CAM5.2</th>
<th>CK7</th>
<th>CK20</th>
<th>NSE</th>
<th>PGP9.5</th>
<th>Chromogranin</th>
<th>Synaptophysin</th>
<th>ER</th>
<th>PR</th>
<th>HER2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
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<td>–</td>
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<td>2</td>
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<td>+++</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Staining: +, weak or focal; ++, moderately strong; ++++, strong diffuse staining.

CK, cytokeratin; ER, oestrogen receptor; NSE, neurone specific enolase; PR, progesterone receptor.

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**Figure 1 (A) Section showing the in situ component in one of the carcinomas. (B) Another in situ component.**
However, some believe that SCNC is a distinct type of breast carcinoma different from the usual types of carcinoma, with variable degrees of neuroendocrine differentiation and carrying a worse prognosis. The presence of an intraductal component with a morphological and immunohistochemical profile similar to the invasive component, as in one of our cases (case 2), lends support to the hypothesis of a primary small cell carcinoma in its own right. Primary SCNC also occurs, as already stated, in many other sites where neuroendocrine cells are normally absent or not readily identifiable, including the ovary and prostate.

The prognostic relevance of neuroendocrine differentiation in breast carcinoma is a subject of debate. Although most studies reported an appreciably worse prognosis, a few did not. This discrepancy may result from non-separation of pure neuroendocrine carcinoma from carcinoma of the usual type with areas of neuroendocrine differentiation. There is no mention of the degree of differentiation in some of the reported cases. In addition, the neuroendocrine component in most of the tumours of the usual type falls into the moderately well differentiated World Health Organisation (WHO) category. Most of the reported pure SCNC cases show an appreciably worse prognosis. Using the WHO criteria, all our cases fall into the poorly differentiated SCNC category.

Size is an important prognostic factor in breast carcinoma in general. Shin et al found that patients with a mean tumour size of 3.2 cm did appreciably worse than those with a mean tumour size of 2.6 cm. The second woman (case 2) in our series with a tumour size of 1.7 cm died within 20 months of diagnosis. The woman with a 1.0 cm tumour (case 1) is alive and free of disease 48 months after diagnosis.

The immunoprofile of epithelial markers in our series is similar to most reported cases. All the tumours showed at least focal positivity for CAM 5.2 and CK7 and were negative for CK20. This is also consistent with the immunoprofile of breast carcinoma of usual types. In contrast, Merkel cell carcinomas are positive for CK20 and negative for CK7, whereas SCNCs of the lung are negative for both markers. This may be useful in differentiating between these tumours.

The expression of neuroendocrine markers by SCNC is inconsistent. Positive expression of oestrogen and progesterone receptors in SCNC of the lung and a few other sites has been reported. Thus, their expression in SCNC is not definite proof of mammary origin. Oestrogen and progesterone receptors were expressed in 67% and 56% of cases reported by Shin et al. All three of our cases were negative for oestrogen and progesterone receptors and HER2.

In summary, SCNC is a distinct type of primary breast tumour. The prognosis may not be as poor as previously portrayed, especially for early stage disease.

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REFERENCES
