Parathyroid hormone related peptide in ovarian carcinoma

Hypercalsciaemia is one of the commonest paraneoplastic syndromes encountered clinically, being associated with an estimated 10–20%, of all solid tumours. Many factors contribute to this syndrome of humoral hypercalsciaemia of malignancy (HMM), including cytokines and prostaglandins of the E series.1 Recently, a peptide structurally and immunologically distinct from parathyroid hormone (PTH), but with parathyroid hormone bioactivity, has been implicated in the pathogenesis of HMM and has been termed parathyroid hormone related peptide or PTHrP.2 Hypercalsciaemia is associated with ovarian carcinoma frequently enough for the ovary not to be ignored as a primary tumour site in women presenting with clinically unexplainable hypercalsciaemia.3 We therefore felt it would be of interest to examine a number of ovarian carcinomas for the presence of PTHrP.

Immunocytochemistry was performed using an antibody raised against the first 34 amino acids of PTHrP (kindly donated by Drs GV Segre and H Jüppner, Boston, Massachussets, USA) and standard indirect immunocytochemical techniques. Two cases of ovarian carcinoma associated with hypercalsciaemia (one small cell and one non-small cell type, supplied by Dr GR Dickerson, Boston) were found to contain PTHrP. PTHrP was present throughout the cytoplasm of the tumour cells but was absent from inflammatory and stromal cells and areas of tumour necrosis. The immunoreactivity was completely abolished when the antibody was pre-incubated with PTHrP (1–34) overnight. Two cases of serous cystadenocarcinoma and two cases of mucinous cystadenocarcinoma of the ovary (from patients who were normalcalcaemic) were found to be negative for PTHrP.

Normal adult ovary does not produce PTHrP, but the peptide has been detected in the human fetal gonad.4 This is the first report of the presence of PTHrP in a hypercalcemic ovarian carcinoma. While the pathophysiological role of PTHrP is yet to be elucidated, one possibility is that in addition to it inducing hypercalsciaemia it may stimulate the growth of tumour cells in an autocrine manner.5 It may also regulate the fetal calcium balance.6

The widespread presence of PTHrP in lung, renal cell, and squamous cell carcinoma and its presence in small cell ovarian carcinoma, as reported here, suggests that PTHrP is a common manifestation of the transformed cell.

Prorenin in ovarian cyst fluid

Aspartic protease renin is secreted by the kidneys and, as the initial enzyme in the renin-angiotensin cascade, is important in the regulation of blood pressure and fluid homeostasis. Recently, high concentrations of the zymogen prorenin have been shown in female reproductive organs.7 The concentrations of prorenin in follicular fluid collected from women undergoing in vitro fertilisation are at least 10 times higher than those in plasma.8 Immunochemical staining has shown that the prorenin is present in the thecal cells lining the follicles from where it is, presumably, secreted into the fluid.9 As only very low concentrations of active renin are found in the ovary, it has been postulated that ovarian prorenin may be biologically active without any necessity for prior removal of the propeptide sequence.10 The role of ovarian prorenin is still unclear but it probably operates through the formation of angiotensin II (AII). Studies with the AII antagonist, saralasin, have indicated a direct role for AII in ovulation,11 and, in addition to its effects on steroidogenesis, the vasoconstrictor and angiogenic properties may be important for follicular growth.

Cysts are commonly derived from the ovarian follicles and frequently contain a large volume of liquid. It was thus considered of interest to determine whether this fluid might also contain a high concentration of prorenin. The fluid from the cysts was removed at laparotomy was collected, stored at −20°C, and assayed for prorenin by the trypsin-activation method of McIntyre et al.12 Renin activity was estimated by measuring the rate of angiotensin I (A1) production from human angiotensinogen.n

Prorenin was detected in the fluid from four of the cysts assayed—three of follicular origin and one from a mucinous cystadenoma.13 Two of the others being virtually negative (table). The concentration of active renin detected in all of the fluids was very low (less than 5% of total) and may have been due to partial activation of the prorenin during collection. This predominance of prorenin over renin is in keeping with previous results for normal ovarian follicular fluid.13

Concentrations of prorenin in ovarian cyst fluid

<table>
<thead>
<tr>
<th>Age</th>
<th>Diagnosis</th>
<th>Prorenin (ng A1/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Follicular cyst</td>
<td>41</td>
</tr>
<tr>
<td>20</td>
<td>Follicular cyst</td>
<td>9</td>
</tr>
<tr>
<td>42</td>
<td>Follicular cyst</td>
<td>24</td>
</tr>
<tr>
<td>44</td>
<td>Mucinous cystadenoma</td>
<td>15</td>
</tr>
<tr>
<td>32</td>
<td>Serous cystadenofibromatous</td>
<td>1</td>
</tr>
<tr>
<td>83</td>
<td>Serous cystadenofibromatous</td>
<td>0</td>
</tr>
</tbody>
</table>


References

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P B Burton, D E Knight, P Quirke, R Smith and C Moniz

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